TACTILE PROCESSING DEPENDS ON MOTOR INTENTIONS

by

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Abstract

Tactile processing serves upcoming actions, which depend on behavioral goals. It remains unclear how neural signals related to movements interact with sensory signals in primary somatosensory (S1) cortex. We developed a cross-modal attention task in which head-fixed mice flexibly switched between responding to tactile stimuli in the presence of visual distractors, or to visual stimuli in the presence of tactile distractors, using licking movements to the left or right side in different blocks of trials. Spiking of S1 neurons during the task showed both tactile and licking-related motor responses. S1 neurons encoded tactile stimuli, licking, and direction of licking in response to tactile but not visual stimuli. Optogenetic stimulation of tongue premotor cortex recapitulated motor signals in S1. Bidirectional optogenetic manipulations revealed that performance depended on sensory-motor activity in S1 during attention to touch but not vision. Our results show that sensory and motor signals interact in S1 to promote specific actions.

Keywords: Sensorimotor processing, pre-motor theory of attention, action schemas, primary somatosensory cortex, barrel cortex, anterior lateral motor cortex.

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Introduction

Whether it be the photons bouncing off this text and onto our retinas or the forces impinging on our skin as we grasp the page on which it is written, we are constantly flooded with information about our external world. To make use of this deluge of stimulation we have evolved incredibly complex sensory systems that sample and process it so that it may be used to inform adaptive behaviors. However, while some of this information relates directly to stimuli that are relevant to our current goals, most of it is either irrelevant, or if acted upon, detrimental to our survival. To further complicate matters, many of the sensory stimuli that are pertinent to our needs in the current moment are often irrelevant in the next. Thus, the flow of incoming sensory information must be discerningly distilled such that only the most critical streams influence our behavior. The details of how our nervous system solves this difficult selection task is still unclear. One potential answer may lie in the interdependence of our sensory and motor systems. In order to optimize the use of information about stimuli, our motor systems are vastly interconnected at multiple levels with our sensory systems. This allows for information to flow from sensory to motor structures such that initiation of adaptive behaviors happens almost concurrently with the processing of sensory stimuli. However, is this trickle of information from multiple sensory to motor structures mirrored by a flow of information from motor to sensory structures? Furthermore, sensory stimuli generally occur in the context of ongoing or specific intended actions. Thus, could connections from motor to sensory structures provide a medium for our intended actions to influence what sensory information gets selected and ultimately perceived?

In this introduction I present an overview of the evidence supporting this possibility, including literature from both the attention and decision-making fields. In addition, I discuss the anatomy and function of the whisker-barrel system in mice to provide the rational for its use as a tool for investigating questions relating to attention and decision making in the present study.

Pre-motor theory of attention

When we direct our attention towards a visual stimulus, we more often than not, center our visual field, or foveate, on that stimulus. Simultaneously attending to and directing our gaze towards a stimulus is normally referred to as overt attention (Moore, Armstrong, & Fallah, 2003). This is a process that is most obvious when we attend towards a relevant moving object. Baseball players keep their "eye on the ball" in order to hit it at just the right time. In doing so, they are both continuously redirecting their gaze as well as their attention while following the ball's moment by moment position in space. An analogous process for overtly attending to tactile information might entail pressing on or brushing one's fingertips over an object or surface of interest. Importantly however, we also have the ability to attend to stimuli without making deliberate movements of sensory organs in order to explore them, a phenomenon usually referred to as covert attention. Visually attending to a stimulus without shifting one's gaze or directing one's attention to a tactile stimulus on our bodies while at rest, are two examples of this process. While there is an obvious behavioral difference between overt and covert attention, it is less clear whether they differ in the underlying mechanisms that govern the selection of relevant stimuli for further processing.

Studies of visual covert attention in primates usually require fixation on a point in space while being cued to attend to a location peripheral to the fixation point. Subjects are then asked to detect or discriminate a target stimulus falling within or outside the attended location (Reynolds & Chelazzi, 2004; Moran & Desimone, 1985; Moore & Armstrong, 2003; Steinmetz & Moore, 2014; Schafer & Moore, 2011; Reynolds, Pasternak, & Desimone, 2000; Schneider & Kastner, 2009; Spitzer, Desimone, & Moran, 1988; Carrasco, 2011). Enhanced behavioral performance, including higher detection or discrimination accuracy as well as shorter reaction times (Carrasco, 2011; Cohen & Maunsell, 2009; Moran & Desimone, 1985; Posner, Snyder, & Davidson, 1980; Reynolds & Chelazzi, 2004; Spitzer et al., 1988; Steinmetz & Moore, 2014), tends to be correlated with stimuli that occur within the attended location. This improved behavioral performance is often accompanied by changes in the firing rate of neurons within the corresponding sensory cortices (Carrasco, 2011; Mitchell, Sundberg, & Reynolds, 2007, 2009; Moore & Armstrong, 2003; Moran & Desimone, 1985; Reynolds & Chelazzi, 2004; Reynolds, Chelazzi, & Desimone, 1999; Reynolds et al., 2000; Schafer & Moore, 2011; Schneider & Kastner, 2009; Spitzer et al., 1988; Steinmetz & Moore, 2014). In one such example, Reynolds, Pasternak, and Desimone showed that attending to a visual stimulus appearing within the receptive field of a recorded V4 neuron caused the neuron to fire more than when the monkey attended away from that location (Reynolds & Chelazzi, 2004). Furthermore, this effect was greatest for low contrast stimuli, suggesting that attention boosts the effective strength of the stimulus rather than causing a multiplicative increase in firing rate. These results suggest that higher evoked firing rates could be underlying the behavioral improvements associated with attention. Similar

attentional effects have been shown for neurons in multiple visual areas, including those at earlier stages of the visual processing stream (Carrasco, 2011; Luck, Chelazzi, Hillyard, & Desimone, 1997; Reynolds & Chelazzi, 2004; Reynolds et al., 1999).

Similar effects on the firing rates of neurons have also been found to occur in the somatosensory system (Hsiao, O'Shaughnessy, & Johnson, 1993; Roy, Steinmetz, Hsiao, Johnson, & Niebur, 2007; Steinmetz et al., 2000). In a study by Hsiao, O'Shaughnessy, and Johnson, monkeys were trained to attend to tactile stimuli while ignoring visual stimuli but then, within the same session, switch to attending to the visual stimuli while ignoring the tactile stimuli (Hsiao et al., 1993). Neurons recorded in both S1 and S2 in these sessions showed higher firing rates while monkeys attended to tactile stimuli compared to when they ignored the tactile stimuli. In a subsequent study using the same task, neurons in S2 were also shown to fire more synchronously to attended tactile stimuli, suggesting an additional mechanism of stimulus selection within this system (Steinmetz et al., 2000).

In cases of overt attention, the ability to detect and discriminate stimuli at attended locations is higher than at unattended locations (Hoffman & Subramaniam, 1995; Rolfs & Carrasco, 2012; Steinmetz & Moore, 2014). The enhanced processing of an overtly attended stimulus may be intuitive given the fact that foveating over the stimulus is by definition exposing the part of the retina with the highest visual acuity to that visual stimulus. However, enhanced processing occurs even before the fovea is able to land on a stimulus of interest (Jonikaitis, Klapetek, & Deubel, 2017; Rolfs & Carrasco, 2012). In one study, participants were instructed to compare the contrasts and orientations of a standard visual stimulus against a test stimulus that would ultimately appear at a cued location on one side of the screen (Rolfs & Carrasco, 2012). Participants first fixated on a location at

the center of the screen, were shown the standard visual stimulus, and after a variable delay were presented a cue telling them to saccade as fast as possible to a location either to the left or right of the fixation point. After the presentation of the cue but before the participants could initiate their saccade, the test stimulus was quickly flashed at the cued saccade location. Importantly, the offset of the test stimulus preceded the onset of the saccade and therefore the stimulus had disappeared before participants could foveate over it. Surprisingly, visual discrimination performance was higher when compared to trials in which the participants were not cued to saccade, suggesting that enhanced processing of the visual stimulus precedes directing one's gaze towards the location of the stimulus.

Despite involving the physical redirecting of one's gaze in one case and the deliberate withholding from shifting of one's gaze in the other, both overt and covert visual attention lead to similar behavioral and neurophysiological changes. Thus, the question remains as to whether they share a common neural mechanism. Furthermore, could this mechanism involve a process that is a necessary precursor for shifting one's gaze in overt attention but terminated early in order to ultimately prevent saccade initiation in covert attention? One line of evidence suggesting a common mechanism comes from studies employing anti-saccade tasks (Steinmetz & Moore, 2014). In this case, monkeys were trained to covertly direct their attention to one location in order to detect a change in a stimulus but are rewarded for reporting this change by saccading to a location opposite the stimulus. As expected V4 neurons showed firing rate modulations to the attended stimuli compared to irrelevant stimuli placed orthogonal to both test stimulus and saccade locations. Surprisingly however, when irrelevant stimuli were placed in the location where monkeys were cued to saccade, V4 neurons also showed enhanced firing rates. Importantly,

this firing rate modulation to stimuli in both test and saccade locations occured within the same individual neurons. These results suggest that the effects of covertly attending to and preparing a saccade in the direction of a stimulus have the same effects on neurons at the level of visual cortex. Further evidence supporting this point comes from work investigating the potential top-down origins of the attentional effects on visual cortical neurons.

While much of the literature has described the modulatory effects of attention on neuronal responses in sensory cortices, the exact mechanism of how these effects are implemented are still a subject of debate. Studies in primates (Bichot, et al., 2015; Ignashchenkova, et al., 2004; McAlonan, Cavanaugh, & Wurtz, 2008; Moore, 2006; Moore & Armstrong, 2003; Moore & Zirnsak, 2017; Rossi, et al., 2007; Schneider & Kastner, 2009; Tremblay, Pieper, Sachs, & Martinez-Trujillo, 2015) and rodents(Halassa & Kastner, 2017; Rodgers & DeWeese, 2014; Schmitt et al., 2017; Wimmer et al., 2015; Zhang et al., 2014) have identified various potential proximal sources for these effects, including but not restricted to, the thalamus (Halassa & Kastner, 2017; McAlonan et al., 2008; Saalmann & Kastner, 2011; Schmitt et al., 2017; Wimmer et al., 2015), motor/pre-motor areas (Cutrell & Marrocco, 2002; Goldberg, Bisley, Powell, & Gottlieb, 2006; Ignashchenkova et al., 2004; Moore & Armstrong, 2003; Mysore, Asadollahi, & Knudsen, 2010; Mysore & Knudsen, 2014; Schafer & Moore, 2011; Schneider & Kastner, 2009; Shomstein & Gottlieb, 2016; Steinmetz & Moore, 2014; Suzuki & Gottlieb, 2013), and the prefrontal cortex (Miller & Cohen, 2001; Moore, 2006; Moore & Armstrong, 2003; Rodgers & DeWeese, 2014; Rossi et al., 2007; Schafer & Moore, 2011; Tremblay et al., 2015; Zhang et al., 2014) . In this introduction I focus mainly on evidence discussing

attentional influences arising from motor/pre-motor areas but for in-depth discussions of the roles of thalamus and prefrontal cortices see (Saalmann & Kastner, 2011) and (Miller & Cohen, 2001) respectively. In the present study we find that stimulus-evoked activity in sensory cortex is enhanced when mice attend to a stimulus. We also investigated whether an upstream cortical region might be acting as a potential source for this top-down enhancement of activity. The method we used to do this was inspired by literature that used the oculomotor system to find that brain areas involved with generating eye movements play an important role in enhancing visual sensory processing, as described below.

The frontal eye field (FEF) region, the lateral interparietal cortex (LIP), and the superior colliculus (SC) in monkeys form a complex interconnected network with visual cortical areas including V1, V2, V4, and MT (Felleman & Van Essen, 1991; Moore, 2006). While FEF (Schiller & Chou, 1998; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000), LIP (Barash, et al., 1991), and SC (Hafed & Krauzlis, 2012; Ignashchenkova et al., 2004; Stryker & Schiller, 1975), are all known to be involved in saccade generation, studies using lesions (Rossi et al., 2007), or reversible inactivations (Bollimunta, Bogadhi, & Krauzlis, 2018; Dias & Segraves, 1999; Lovejoy & Krauzlis, 2010; Wardak, Olivier, & Duhamel, 2004) have also heavily implicated them as being important for spatial attention. Furthermore, activity within these areas show similar modulation in spiking activity as visual cortical neurons in attention tasks (Bisley & Goldberg, 2003; Ignashchenkova et al., 2004; Thompson, Bichot, & Sato, 2005; Zhou & Desimone, 2011). Perhaps the most convincing evidence suggesting these motor/pre-motor areas are a primary source of attentional modulations of sensory cortex comes from studies using micro-stimulation (Armstrong & Moore, 2007; Clark, Armstrong, & Moore, 2011; Cutrell & Marrocco, 2002;

Moore & Armstrong, 2003). In line with their role in generating eye movements, it has been known for decades that electrically stimulating FEF and SC can reliably induce saccades (Bruce, et al., 1985; McHaffie & Stein, 1982; Stryker & Schiller, 1975) . To test to see if firing rate modulations in V4 could be caused by top-down influences from FEF, Moore and Armstrong microstimulated FEF while monkeys were performing a spatial attention task (Moore & Armstrong, 2003). To first map regions within FEF that were retinotopically aligned to concurrently recorded V4 neurons, the experimenters induced saccades by electrically stimulating areas in FEF at suprathreshold levels. They then found that if they electrically stimulated these same areas but at a level that was sub-threshold for generating saccades, they could mimic attentional effects on the firing rates of V4 neurons. Specifically, microstimulation of FEF would generally cause neurons in V4 to fire more when stimuli of a preferred orientation were placed in the neurons' RFs. If no stimulus was presented in the neurons' RFs or if the stimuli were of a non-preferred orientation, microstimulation was ineffective at enhancing firing rates. These studies not only provide evidence that motor/pre-motor areas are important for generating attention-like effects but also support the hypothesis that covert and overt attention rely on a common mechanism.

Reminiscent of much of the above work done in primates, studies looking at the midbrain stimulus selection network of the barn owl have provided important evidence that oculomotor regions playing critical roles in spatial-attention is shared across species (Knudsen, 2018; Mysore et al., 2010; Mysore & Knudsen, 2014). A central structure of this network, the optic tectum (OT; SC in mammals) and its connections with nucleus isthmi pars magnocellularis (Imc) in the tegmentum, is known to be critical for giving rise to a retinotopically aligned saliency map. Retinotopically distributed neurons in OT send

projections to retinotopically aligned regions of Imc. In return, inhibitory neurons in the Imc send long-range connections broadly to regions of OT. Imc neurons also mutually inhibit other inhibitory neurons in neighboring regions within the Imc. This pattern of connections makes up a circuit that has been found to support a process of reciprocal inhibition of feedforward lateral inhibition (Mysore & Knudsen, 2012). The implications of this for sensory processing is that it allows for the competition and ultimately selection of stimuli to occur globally across retinotopic space. For example, Mysore, Asadollahi, and Knudsen found that responses to a looming visual stimulus in the RF of an OT neuron was suppressed if it was presented simultaneously with a similarly salient competitor stimulus (Mysore et al., 2010). This was true regardless of where the competitor stimulus appeared relative to the RF of the neuron in retinotopic space. Importantly it was found that top-down influences from forebrain areas could dramatically bias this global saliency map. The arcopallial gaze field (AGF) in the owl's forebrain in many ways serves a similar role as the FEF of primates. In particular, like the FEF, the AGF is involved in gaze control (Knudsen, Cohen, & Masino, 1995) and can change the effective salience of a stimulus in OT if microstimulated (Mysore & Knudsen, 2014). Work from the same group showed that microstimulating areas in AGF that have aligned RF with neurons in OT can cause those OT neurons to fire more to looming stimuli located within their RFs (Mysore & Knudsen, 2014). Furthermore, stimulating non-retinotopically aligned regions in AGF causes OT neurons to decrease stimulus-evoked firing, thus mimicking the effects of presenting a strong competitor stimulus outside the RF of the neuron.

Attention and choice probability

A major effect observed in the present study shows that enhanced stimulus-evoked firing rates occur whenever the mouse makes a decision or correctly reports the onset of a stimulus. This effect is something that has been observed in decision making studies in both non-human primates (Britten et al., 1996; Nienborg & Cumming, 2006, 2009; Nienborg, R. Cohen, & Cumming, 2012; Palmer, Cheng, & Seidemann, 2007; Romo & de Lafuente, 2013) and mice (Kwon, Yang, Minamisawa, & O'Connor, 2016; Otazu, Tai, Yang, & Zador, 2009; Sachidhanandam et al., 2013; Yamashita & Petersen, 2016; Yang, Kwon, Severson, & O'Connor, 2016). A significant portion of this literature concerns the topic of "choice-probability". Surprisingly, there is a large apparent overlap between studies of choice probability and studies of attention, despite not traditionally being thought to be directly related. Here, were review the commonalities between these topics as they relate to the present study.

In 1996, Britten and colleagues trained monkeys in a two-alternative forced-choice task where monkeys were required to indicate the direction of a random moving dot stimulus (Britten et al., 1996). In order to classify a stimulus, monkeys had to saccade to a location that corresponded to the direction that they judged to be the average direction of the moving dots. While monkeys were performing this task, neurons were recorded in the middle temporal visual area (MT) Importantly, neurons in MT are known to be responsive to stimulus movement in a specific "preferred" direction (Maunsell & Van Essen, 1983). While the monkeys easily discriminated the mean direction of the dots when most or all of the dots moved in the same direction (~100% coherence between dots), their ability to

discriminate mean movement direction dropped as the movement coherence decreased. When the coherence of the stimuli was near 0%, the the movement direction indicated by the monkeys' fell to chance levels, creating a particularly useful comparison between trials where the monkey classified a stimulus as moving in one direction with trials where they classified the *same* stimulus as moving in the opposite direction. Results showed that MT neurons fired more on average when the monkey made a saccade in line with neuron's preferred direction. A receiver operating characteristic (ROC) analysis was performed to show that this was true on a trial-by-trial basis. The resulting metric, the area under the ROC curve (AUC)ranges from 0 to 1. An AUC value close to 1 indicates a high probability that an ideal observer can correctly categorize the firing rate of a neuron as having been recorded from a trial where the monkey made a specific decision. An AUC value of 0.5 indicates that the probability of correct categorization is at chance level while a value close to 0 indicates below chance performance. Neurons showing AUC values significantly higher than chance are informative about the behavioral choice of a monkey on a trial-by-trial basis and thus are said to have significant "choice probability". Activity in various other visual cortices, including V1 (Palmer et al., 2007) and V2 (Nienborg & Cumming, 2006, 2009), have also been found to show significant choice probability activity.

While studies of choice probability normally employ a two-alternative forced-choice task, where subjects are required to respond (move) in one direction or another, others have instead used detection tasks (Bosking & Maunsell, 2011; Price & Born, 2010). In this case, subjects are required to indicate whether a near-threshold stimulus has appeared or changed. Thus, trial outcomes consist either of the execution or withholding of a response. ROC analyses performed on these data result in a similar metric termed

"detect probability" or the ability of an ideal observer to correctly predict, using the firing rate of a neuron on a trial-by-trial basis, whether the subject has detected the stimulus.

One similarity between studies of attention and choice/detect probability is that stimulus presentation overlaps in time with the intention to make a stimulus-dependent overt movement. Additionally, in both cases, a similar modulation of neural responses in sensory cortices is thought to influence the processing of the stimulus and ultimately the decision of the animal. Thus, it at least seems possible that the same mechanisms may underlie the phenomena observed in each case. Since most studies on choice/detect probability and the motor/pre-motor mechanisms of attention have been done in either monkeys or barn-owls, loss of function studies with a high temporal and spatial resolution (such as is possible with optogenetics and related methods) have so far been difficult. Without such experiments, a full account of the necessity of these firing rate modulations for enhanced sensory processing will be difficult to achieve. With the advent of cell type specific optogenetics and the development of complex head-fixed behaviors in mice, this is a problem that may be resolved using the mouse as a model organism. Furthermore, due to the relatively well described interconnected nature of the primary somatosensory and motor systems in the mouse, the whisker-barrel system could prove to be an ideal tool for investigating these topics.

Sensorimotor integration in barrel cortex

Most animals have evolved sensory systems that specialize in processing information from five general modalities: vision, olfaction, audition, gustation, and touch. Perceiving a tactile stimulus very often requires sensorimotor integration. Whether it be a person applying pressure on a piece of fruit to infer how ripe it is, or a mouse avoiding open spaces by rhythmically palpating the surfaces around it, both tactile and motor information are key factors governing these behaviors.

For rodents, much of the important tactile information about their surroundings is extracted using their vibrissae or whiskers. 35 of these long, tapered hairs are embedded in large follicles that are arranged in a grid-like fashion on either side of the mouse's face. Within the follicles lie an assortment of specialized receptors (Abraira & Ginty, 2013). Each of these receptors is innervated by afferent nerve endings from cells that originate in the trigeminal ganglion (TG). The deflection of a whisker, either by the active palpitation of objects or by the passive contact with moving stimuli, exerts mechanical forces on these receptor-afferent complexes. Depending on the type of receptor, a subset of these forces is encoded into spiking activity of the associated afferent. For example, the spiking activity of TG neurons that innervate Merkel cells was found to carry information about the bending moment and the rate of change of this moment during active touch (Severson et al., 2017). These Merkel-afferents were also found to transmit information relating to the inertial moment of the whisker during whisking in air.

In addition to their peripherally projecting afferent endings, TG cells also extend processes centrally towards different nuclei in the brainstem. Multiple parallel pathways beginning in these brainstem nuclei then carry tactile information to cortical neurons via

cells in the thalamus (Veinante & Deschênes, 1999). One of these pathways, the lemniscal pathway, carries information about whisking and touch (Yu et al., 2006) first to the principal trigeminal nucleus (PrV), then to the ventral posteromedial nucleus of the thalamus (VPM), and ultimately to spiny stellate neurons in layer 4 of whisker primary somatosensory cortex (S1) (Deschênes et al., 2005) . Importantly, information that ascends from the whisker follicle to layer 4 of S1, does so in a somatotopic way such that neurons in S1 that respond to deflections of the same whisker are generally located in close proximity to one another (Woolsey & Van der Loos, 1970). This somatotopic grouping of cells is nicely visualized histologically whereby neurons responding to the same whisker are shown to be aggregated in rounded structures that are reminiscent of barrels. These barrel structures occur in a grid-like fashion that mirrors the distribution of whiskers across the contralateral whisker pad of the mouse. Indeed, each of the barrels corresponds to an individual whisker such that neurons in neighboring barrels respond to deflections of neighboring whiskers. The distinct histologic visualization of the topographic structuring in the whisker region of S1 is unique, leading this part of cortex being named "barrel-cortex" (Woolsey & Van der Loos, 1970). Furthermore, the easily visualized somatotopy within S1 also exists throughout the lemniscal pathway such that neurons within PrV occur in "barrelettes" and neurons within VPM thalamus are arranged in "barreloids" (Veinante & Deschênes, 1999).

After first reaching layer 4 of S1, sensory information originating from a single whisker generally begins by spreading in directions orthogonal to the surface of cortex (Lefort, Tomm, Floyd Sarria, & Petersen, 2009; Lübke & Feldmeyer, 2007). Layer 4 neurons excite pyramidal neurons in layers 2/3 which in turn activate excitatory neurons in

layers 5 and 6. This relatively circumscribed inter-layer processing functionally defines a cortical column, a motif that is seen across many sensory cortical areas (Hubel & Wiesel, 1962; Mountcastle, 1957). Importantly, the pattern of activity across a cortical column is by no means restricted to this canonical motif. For example, VPM neurons are also known to project and excite cells within layer 6 (Beierlein & Connors, 2002), neurons within the posteromedial nucleus of the thalamus (POM) innervate layers 2/3 and 5 (Bureau, Paul, & Svoboda, 2006; Williams & Holtmaat, 2019), while pyramidal neurons in layer 2/3 as well as 5 are known to project to proximal as well as distal regions outside the barrel column (Aronoff et al., 2010; Mao et al., 2011). This increasing degree of promiscuity as activity percolates through the different layers of cortex was impressively shown using VSD (Aronoff et al., 2010; Ferezou et al., 2007), two photon calcium imaging (Peron, Freeman, Iyer, Guo, & Svoboda, 2015), and electrophysiological recordings (Petersen & Sakmann, 2001) in which passive single whisker deflections in awake mice strongly activated the corresponding barrel but was shortly followed by a spread of activity to neighboring barrels. Furthermore, in quietly awake mice, passive whisker deflections ultimately evoked activity in more distal cortical regions in which whisker secondary somatosensory cortex (S2) and whisker primary motor cortex (M1) were the most prominent (Aronoff et al., 2010; Ferezou et al., 2007).

The whisker-barrel system is often thought to be primarily a sensory system, specializing in conveying tactile information from a mouse's environment to higher cortical regions for further processing. However, a purely "sensory" view of the system is not correct, as it neglects a large body of evidence that shows that motor structures interact with the processing of sensory information at multiple levels. In line with the

demonstration that passive whisker deflections cause activity to spread from barrel cortex to distal cortical areas, anatomical studies have shown that neurons within barrel cortex send dense projections to multiple motor regions including dorsal striatum (Aronoff et al., 2010; Hintiryan et al., 2016), M1 (Aronoff et al., 2010; Mao et al., 2011), as well as whisker secondary motor cortex (M2) (Barthas & Kwan, 2017; Reep et al., 1987.). Similarly, barrel cortex(Lee et al., 2013; Mao et al., 2011) as well as other early somatosensory cortices (Manita et al., 2015) are known to receive dense projections from motor regions, implying multiple sensorimotor feedback loops. These reciprocal anatomical connections have important functional implications that suggest a tight coordination between early whisker sensory areas and downstream motor regions.

Exemplifying this tight functional sensorimotor coordination, one study showed that brief optogenetic stimulation of S1 during quiet wakefulness could cause mice to begin bouts of exploratory whisking. However, if M1 was first inhibited using muscimol, this same stimulation procedure of S1 was ineffective in generating exploratory whisking (Sreenivasan et al., 2016). Perhaps demonstrating a complementary interaction that can drive bouts of whisking, it was found that strong optogenetic activation of M1 caused whisker protraction while strong activation of S1 caused whisker retraction (Matyas et al., 2010; Sreenivasan et al., 2015). In another study, projections from whisker M1 onto vasoactive intestinal polypeptide expressing interneurons (VIP) in barrel cortex were shown to mediate disinhibition of the distal dendrites of S1 pyramidal neurons, introducing an additional lever of control of M1 over tactile processing in S1 (Lee et al., 2013). Interestingly, motor cortex was also found to influence sensory transmission of tactile information at the level of thalamus. In rats, Urbain and Deschênes showed that M1

stimulation inhibited neurons within the ventral division of the zona incerta (ZIv), a subthalamic region that sends inhibitory projection to POM(Urbain & Deschênes, 2007). Since both S1 (Bureau et al., 2006; Williams & Holtmaat, 2019) and S2 (C. C. H. Petersen, 2007) receive tactile information from POM, these results suggest that M1 may be playing a role in permitting sensory input to cortex via a disinhibitory mechanism.

Demonstrating that these dense anatomical connections between sensory and motor areas provide a medium for top-down influences on sensory processing, Xu and colleagues showed that integration of sensory and motor signals can have a dramatic non-linear effect on the activity of neurons in barrel cortex (Xu et al., 2012). Specifically, using two photon calcium imaging and whole cell recording of dendrites, they found that a large prolonged dendritic calcium influx and electrical depolarization in layer 5 neurons only occurred when mice contacted a pole while actively whisking. Whisking alone or passive whisker deflection did not have the same effects. Furthermore, despite contacting the pole with similar forces, calcium signals in S1 dendrites were abolished when M1 was inhibited with muscimol. Since they are known to have large effects on firing rates (Larkum, Zhu, & Sakmann, 1999; Takahashi et al., 2016), these prolonged dendritic calcium spikes in barrel cortex neurons likely play a key role in sensory processing. Consistent with this, a subsequent study by the same group showed that dendritic calcium spikes are required for individual layer 5 neurons in barrel cortex to fire selectively for the location of contacted objects (Ranganathan et al., 2018). Furthermore, they showed that this selectivity results from non-linear mixing of information about the magnitude of touch (intensity of the stimulus) and the whisker angle (a motor related signal).

Active directed whisking over an object is in many ways analogous to foveating over a visual stimulus. In both cases, sensory receptors are moved in order to better expose them to a stimulus of interest. Since, in the visual system, attentional mechanisms are closely associated with gaze shifts towards a stimulus, it is possible that when rodents move their whiskers in a directed manner, they are engaging similar attentional processes. Furthermore, just as visual covert attention seems to be co-opting processes that lead up to gaze shifts, perhaps mice also co-opt processes leading up to directed whisking for attentional purposes. Evidence for this comes from a study that showed that large dendritic calcium influxes are not just restricted to active directed whisking but were also present in a detection task(Takahashi et al., 2016). The authors showed dendritic events similar to those found by Xu and colleagues only occurred when head-fixed mice correctly detected a brief whisker deflection. Failure to detect the stimulus was correlated with a distinct absence of strong dendritic calcium events. Furthermore, blocking these events by selectively inhibiting the dendrites of layer 5 neurons caused mice to fail to detect the stimulus. While the origins of dendritic calcium events in active whisking were found to depend on M1 input. Whether this is true in the passive whisker detection task was not directly investigated. Together these results suggest that top-down inputs from motor regions strongly modulate bottom-up sensory signals in barrel cortex when mice actively contact objects and that this may also be true during detection of passive whisker deflections. This, coupled with the interdependence of somatosensory and motor systems in the mouse suggests that barrel cortex could prove to be a very useful model for investigating the mechanisms underlying motor/pre-motor sources of attention and choice-related activity.

Barrel cortex as a model for choice-related activity and attention

If attention and choice-related enhancements of activity in sensory cortex do in fact share a common mechanism, then recent work investigating choice related activity in mice provides further motivation for using barrelcortex as a tool to investigate attentional processes. In a study from Sachidhanandam and colleagues, head-fixed mice were trained to report a brief, low-intensity whisker deflection by licking a reward port (Sachidhanandam et al., 2013). In a majority of trials, mice were able to correctly report the presentation of the stimulus, resulting in "hit" trials. However, mice failed to detect the same stimulus in a minority of trials, resulting in "miss" trials. Whole-cell recordings in barrel cortex during behavior showed that neural activity was enhanced during hit trials compared to miss trials, demonstrating that S1 neurons show strong detect probability. This enhanced activity only became evident ~50-100 ms after the onset of the stimulus but continued for several hundreds of milliseconds. Importantly, inhibiting S1 during this delayed enhanced response impaired the ability of mice to detect the stimulus. These results were replicated and extended to show that these firing rate modulations were absent in TG and VPM neurons (Yang et al., 2016) but present in S2 (Kwon et al., 2016), suggesting that the enhancement of activity in sensory cortex likely originates from top-down input.

While the above results suggest that modulatory effects on sensory processing within S1 are likely originating from top-down inputs, the exact source of these inputs are still not fully defined. Due to its earlier mentioned role in enhancing dendritic activity when a mouse actively whisks against an object, one potential source could be M1. However, another candidate region that could be playing a role in this activity is M2. Manita and colleagues showed that S1 and M2 show dense reciprocal connections with one another

(Manita et al., 2015), a finding supported by previous work (Reep et al., 1987.). They then showed that stimulation of the forepaw of a mouse led to an early phase of evoked activity in S1, followed shortly by a sensory evoked response in M2, and finally by a second phase of prolonged activity in S1 occurring >50 ms after stimulation. Using calcium imaging, this activity was also confirmed to be activating dendrites of layer 5 neurons in S1. When the experimenters again stimulated the forepaw while blocking M2 using tetrodotoxin (TTX), the first phase of sensory evoked activity was still present but the second phase of activity in S1 was absent. Furthermore, stimulating the forepaw of the mouse while inhibiting M2 axons in S1 led to fewer stimulus evoked movements, suggesting either impaired perception of the stimulus or an impaired ability to respond to the stimulus.

In the oculomotor system, motor regions involved with generating saccades directly lead to firing rate modulations in sensory cortices, as discussed earlier. The important distinction between these results and those in which barrel cortex activity is enhanced during detection tasks is the movements produced during behavior. In the case of the oculomotor system, monkeys are moving their eyes in order to shift their gaze to perceive a visual stimulus or to report a decision. In this case, the part of the animal's body that is moving is the same one that it is using to sample the sensory stimulus. When mice detect a whisker deflection, they are licking a reward spout to report the onset of the stimulus. In this case, the movement being performed is using a body part that is distinct from the one it is using to sample the stimulus. This distinction could lead to significant differences in the origins of the top-down influence on sensory activity. One finding that points to a different source of top-down input when mice report a decision by licking was shown in a recent study (Allen et al., 2017). Mice were trained to report the detection of an olfactory

stimulus by licking a water port. When experimenters used widefield calcium imaging of a large part of the dorsal surface of cortex, they found that a wave of activity covered most of the imaged area, including barrel cortex. A similar observation was made in a study that had mice report the detection of a tactile stimulus (Chen et al., 2017). In both cases the wave of activity seemed to originate in a region called the anterior lateral motor (ALM) region, a part of M2 that has specifically been associated with tongue movements. Allen and colleagues found that blocking ALM activity leads to impairments in the mice's ability to report the onset of the stimulus and abolished the previously observed wave of activity. Reminiscent of some of the oculomotor literature we reviewed earlier, the experimenters also showed that electrical stimulation of ALM in untrained mice led to tongue protrusions. These results suggest that ALM may be the original source of the top-down input to barrel cortex when mice detect whisker deflections.

While the work discussed in this introduction has contributed greatly to the goal of understanding how our nervous system prioritizes the processing of certain sensory information, a full explanation of this mechanism still eludes us. Work done in both the decision-making and attention fields suggest that information about certain stimuli is enhanced in sensory cortices. And while this has been done in studies relating to choice/detect-probability, direct loss-of-function studies would be required to fully demonstrate the necessity of firing rate modulations in attention. Studies in non-human primates and barn owls strongly indicate that top-down mechanisms from specific motor regions are playing a major role in causing these enhanced responses. However, when the intended motor actions and the sampling of associated sensory information are carried out by different parts of the body, the origin of this top-down input becomes less clear.

Furthermore, when mice make a stimulus-dependent movement, motor areas governing the movement seem to broadcast a top-down signal that covers multiple sensory cortices. Thus how, if at all, does this signal enhance the processing of information about specific sensory stimuli and not others? These are issues that need to be worked out if we are to understand how attention is generalized to affect all stimulus-response associations.

In the present study we set out to better understand the mechanisms that underly how sensory information is enhanced in barrel cortex when mice selectively attend to tactile stimuli. To do this we designed a novel cross-modal attention task for head-fixed mice that requires different actions to be taken in response to a tactile or visual stimulus, depending on the context. In different blocks of trials, mice responded either to a weak tactile stimulus while ignoring visual distractors, or to a weak visual stimulus while ignoring tactile distractors. Detection of each stimulus modality required a distinct licking-based action. We hypothesized that the sustained intention to make a specific motor action for a tactile stimulus would enhance activity in barrel cortex shortly after the onset of the tactile stimulus presentation. This enhanced activity would also be required for the detection of the stimulus and thus blocking it would degrade behavioral performance. Despite not governing the movements of the appendages collecting the sensory information (whiskers), we further hypothesized that this enhanced activity would originate from tongue premotor/motor areas that are involved with the intention to execute the action upon stimulus presentation. Although this top-down signal originating from tongue premotor cortex has been shown to spread widely across cortex (Allen et al., 2017; Komiyama et al., 2010; Li, et al., 2015), we reasoned that the interaction between simultaneously occurring

sensory and motor information in barrel cortex would interact synergistically in a way that may underly the specificity required for the behavioral effects of attention.

We found that S1 activity reflected tactile sensory responses but was also enhanced by activity that reflected licking-related movements. Elevated activity was strongest and earliest in neurons that encoded both sensory and motor related signals, suggesting a synergistic interaction. A subset of neurons was selective for the direction of licking in response to tactile but not visual stimuli, with responses that were further enhanced by licking toward the same side as the contralateral whisker stimulus, indicating specific synergy for hemispherically matched sensory and motor processing. Suggesting a possible source of the enhanced activity observed during behavior, microstimulation of tongue premotor cortex recapitulated motor-related task activity in untrained mice, even in the absence of overt movement. Optogenetic excitation of S1 promoted responding during tactile but not visual blocks of trials. Similarly, optogenetic inhibition of sensory-motor activity in S1 greatly reduced task performance during tactile but not visual blocks of trials. Thus, activity was read out from S1 to enable tactile- but not visually-guided behavior.

Our results support the hypothesis that attentional modulation of neuronal activity in somatosensory cortex has a premotor origin and demonstrate that the actions associated with sensory stimuli shape tactile processing via mixing and selective readout of sensory and motor signals.

Experimental Procedures

Mice.

All procedures were performed in accordance with protocols approved by the Johns Hopkins University Animal Care and Use Committee. Ten male mice included in behavioral and optogenetic inhibition experiments were obtained by crossing PV-IRES-Cre (Jackson Labs: 008069; B6; 129P2-Pvalb$^{tm1(cre)Arbr}$/J) (Hippenmeyer et al., 2005) with Ai32 (Jackson Labs: 012569; B6;129S-Gt(ROSA)26Sor$^{tm32(CAG-COP4*H134R/EYFP)Hze}$/J) (Madisen et al., 2012) lines. Eight male mice included in behavioral experiments were obtained by crossing SOM-IRES-Cre (Jackson Labs: 013044; Sst$^{tm2.1(cre)Zjh}$/J) (Taniguchi et al., 2011) with Ai32 lines. Seven Emx1-Cre (Jackson Labs: 005628; B6.129S2-Emx1$^{tm1(cre)Krj}$/J) (Gorski et al., 2002) mice included in optogenetic activation of ALM and S1 experiments were crossed with Ai32 mice. All mice ranged in age from 8 to 32 weeks old and were housed in groups of up to five in a vivarium with reverse light-dark cycle (12 h each phase). Mice were singly housed after surgery and during behavioral experiments. Details of assignment to different experimental conditions are detailed in Table S1.

Behavioral tasks.

All behavioral experiments were conducted while mice were head-fixed. The behavioral apparatus was controlled by BControl software (C. Brody, Princeton University). 7-10 days after surgery and 7-14 days before behavioral training, mice were allowed ~1 ml of water daily until reaching ~70% of their starting body weight. On training days, mice

were allowed to perform the task until sated and were weighed before and after each session to determine the amount of water consumed. Additional water was given if mice consumed <0.3 ml of water.

Stimulus-training. On the first day of training mice were acclimated to head fixation in the behavioral apparatus while being given free access to water via two reward ports located 6-10 mm and ~35 degrees to the left and right of the mouse's midline. On all subsequent training days, a single whisker (always on the right whisker pad) was threaded into a glass pipette that was attached to a piezo actuator (D220-A4-203YB, Piezo Systems) driven by a piezo controller (MDTC93B, Thorlabs). ~1.5 mm of whisker remained exposed at the base. For ~1-3 days, mice were given a drop of water (~6 µl) for licking the right reward port after the onset of a tactile stimulus (sinusoidal deflections at 40 Hz, 1 s, ~1400 deg/s). Licks that occurred within 0.1 s from stimulus onset were not rewarded but any subsequent licks that occurred between 0.1 s and 1.5 s were rewarded. Licks occurring in a 0.2 s period prior to stimulus onset resulted in the withholding of the stimulus presentation for that trial and no reward or punishment being given. The length of the trial and the subsequent inter trial interval remained the same despite the withholding of the stimulus. Trials with dropped stimuli were removed from later analysis. For the next ~1-3 days mice were presented with visual stimuli (1 s blue LED flash, p = ~50 mW at the tip of an 0.22 NA, Ø105 µm optic fiber M43L01, Thorlabs, located 5.5 cm away from the tip of the mouse's nose along the midline; LEDD1B, Thorlabs) and given a drop of water for licking the left reward port until they began to reliably detect the stimuli. Following this stimulus-training, training in the cross-modal attention task began.

Cross-modal attention task. Throughout a behavioral session, mice were exposed to randomly interleaved trials where either one of two tactile (0.05 s or 0.15 s sinusoidal deflections at 20 Hz, ~800 deg/s) or one of two visual stimuli (0.05 s or 0.15 blue LED flash, ~3 mW at tip of fiber optic) was presented (inter stimulus interval: 3.5 s fixed interval + random interval drawn from an exponential distribution with a 4 s mean). Within a session, trials were grouped into either tactile or visual blocks (~80 trials per block, 3-5 blocks per session). In tactile blocks, mice were rewarded with a drop of water for licking the reward port located to the right of the mouse following tactile but not visual stimuli. Mice were also not rewarded if they licked the reward port located to the left of the mouse at any point within tactile blocks. In visual blocks of trials mice were rewarded if they licked the reward port located to the left of the mouse following visual but not tactile stimuli. They were also not rewarded for licking the reward port located to the right of the mouse at any point during visual blocks. Blocks were not overtly signaled to the mouse with an external sensory cue following a block switch. Mice were allowed ~10 trials to switch responding to the correct stimulus through trial and error. If mice failed to switch after ~10 trials they were assisted by manual release of a water at the correct reward port following a correct stimulus by the experimenter. After ~10-20 days of training the difficulty of the stimuli were increased (Tactile, 0.05 s or 0.15 s sinusoidal deflections at 20 Hz, ~600 d/s; Visual, 0.05 s or 0.15 s blue LED flash attenuated to ~$3x10^{-3}$ mW from the tip of the optic fiber using ND filters, ND = 3, NE530B Thorlabs). Licks to the correct reward port following tactile stimuli in tactile blocks or visual stimuli in visual blocks were marked as "Hit" trials. Failure to lick to the correct port after tactile stimuli in tactile blocks or visual stimuli in visual blocks were marked as "Miss" trials.

Licks to either reward port after tactile stimuli in visual blocks, visual stimuli in tactile blocks, or to the incorrect reward port after either stimuli were marked as "False alarm" trials. Withholding licking after tactile stimuli in visual blocks or visual stimuli in tactile blocks were marked as "Correct rejection" trials. Performance in the task was measured using percent correct:

$$\frac{(\#\ Hits\ +\ \#\ Correct\ rejections)}{Total\ \#\ of\ trials}$$

Training continued until mice achieved a performance of >70% for at least two days. After reaching criterion performance mice were given an additional ~17 test sessions for S1 recordings. Days in which overall performance was <65% or where performance within tactile blocks or visual blocks was <60% were dropped and not used for further analysis.

Direction reversal task. Two additional block types were added during test sessions in 4 mice trained on the cross-modal attention task. In tactile-lick-direction-control blocks, mice were rewarded for licking to the left reward port after tactile stimuli. No visual stimuli were presented, and no reward was given for licks to the right reward port. In visual-lick-direction blocks, mice were rewarded for licks to the right reward port after visual stimuli. No tactile stimuli were presented, and no reward was given for licks to the left reward port. Mice either began a test session with lick-direction-control blocks followed by normal tactile and visual blocks or began a test session with visual and tactile blocks followed by lick-direction-control blocks.

Surgery.

Microdrive implantation. All mice used were implanted with titanium headposts (O'Connor et al., 2013). Briefly, mice were anesthetized (1%–2% isoflurane in O_2; Surgivet) and mounted in a stereotaxic apparatus (David Kopf Instruments). Body temperature was maintained with a thermal blanket (Harvard Apparatus). The scalp and periosteum over the dorsal surface of the skull were removed. The skull surface over the posterior half of the left hemisphere which covers S1 was left untouched. The remaining exposed area of the skull was scored with a dental drill and the head post affixed using cyanoacrylate adhesive (Krazy Glue) followed by dental acrylic (Jet Repair Acrylic). Mice were then implanted with microdrives (J. Y. Cohen, Haesler, Vong, Lowell, & Uchida, 2012) coupled to optic fibers (200 μm diameter, 0.39 NA) after a ~0.5 mm craniotomy. For S1 recordings, electrodes were targeted to -1.4 mm posterior and 3.8 mm lateral to bregma. Microdrives were fixed in place using dental acrylic.

Optic fiber implantation above anteriolateral motor area (ALM). Headposts described above were modified in order to leave a larger area of the dorsal surface of the skull exposed. Craniotomies were targeted to ALM (+2.5 anterior, +1.5 lateral to bregma) bilaterally. Using dental acrylic, optic fibers (200 μm diameter, 0.39 NA) were fixed in place above ALM such that their tips were suspended <1 mm above the surface of the exposed cortex. The skull surface over the posterior half of the left hemisphere which that includes S1 was left untouched but otherwise dental acrylic was used to cover up the remaining exposed skull.

Clear skull preparation for S1 activation. Modified headposts that leave a large area of the dorsal surface of the skull exposed were fixed to the skull of the mice using adhesive luting cement (C&B Metabond Quick Adhesive Cement System; Parkell). An additional layer of adhesive luting cement was applied to the entire surface of the exposed skull to achieve a high degree of transparency.

Electrophysiology.

Tetrode microdrives. For S1 barrel cortex recordings in the cross-modal attention task, we recorded extracellularly from multiple neurons simultaneously using custom built 8-tetrode (each tetrode consisting of four electrodes wound together) 200-µm-opticfiber-screw-driven microdrives. The tetrodes were fixed with cyanoacrylate to the side of the optic fiber such that 900 µm extended past the tip of optic fiber. The optic fiber was then itself fixed to the base of the microdrive using epoxy (5 min epoxy; Devcon). Microdrives were implanted into S1 at ~35 degrees from vertical and as superficially as possible. After each day of recording in the cross-modal attention task we advanced the tetrodes ~75 µm in order to sample from a new set of neurons on the subsequent day of recording.

Silicon probes. 64-channel linear probes (ASSY-77 H3, Cambridge NeuroTech) were used for silicon probe recordings and coated with DiI to histologically verify the site of recording post-hoc. On the day of recording (>3 hr before the start of recording), a craniotomy was made over left S1 (-1.4 mm posterior and 3.8 mm lateral to bregma) and subsequently covered with a silicon casting compound (Kwik-cast sealant). The probe was inserted into cortex at ~40 degrees from verticaland left for 10 min before recording

to allow for tissue relaxation. After microdrive implantations or silicon probe insertions, whiskers on the whisker pad contralateral to the side of recording were manually stimulated while monitoring spiking activity. Whiskers that elicited the largest responses from the most neurons were used for subsequent experiments while all other whiskers were cut close to their base.

Data analysis. Neural signals and behavioral timestamps were recorded using an Intan recording system (RHD2000 series multi-channel amplifier chip; Intan Technologies). Broadband signals from all electrodes or probe contacts were filtered between 0.09 Hz and 7.6 kHz and sampled continuously at 30 kHz. Neural signals were bandpass filtered between 700-6,000 Hz and spikes from microdrive recordings were sorted offline using MClust software (MClust by A. David Redish) while spikes from silicon probe recording were sorted using Kilosort (Pachitariu, et al., 2016). Neurons were excluded in further analysis if the rate of ISI violations within a 2 ms window was >1%, L-ratios were >0.07. Neurons were also excluded if spike rates across a session showed a qualitatively obvious drift or if spike waveforms showed unstable shapes after visual inspection.

ALM stimulation.

Naïve untrained Emx1;Ai32 mice with optic fibers implanted over ALM and craniotomies over left S1 were head-fixed in the same apparatus used for behavioral experiments. Prior to silicon probe insertion and electrophysiological recording, the following procedure was performed in order to identify the appropriate parameters for optogenetic stimulation of ALM. ALM was stimulated bilaterally using 10 Hz square

pulse trains lasting 1.5 s. LED amplitude was systematically varied from pulse train to pulse train while tongue protrusions and general facial movements were visually monitored. Three LED amplitudes were selected that generated increasing levels of behavioral activity. The lowest LED amplitude (~1 mW at optic fiber tip) that resulted in no visually detectable tongue protrusions or facial movements was selected for level 1 stimulation parameters. LED amplitudes (3-7 mW at optic fiber tip) that generated moderate facial movements in all stimulation trains as well as tongue protrusions in a minority of stimulation trains were selected for level 2 stimulation trials. The lowest LED amplitudes (9-13 mW at optic fiber tip) that generated vigorous facial movements and tongue protrusions in the majority of stimulation trains were selected for level 3 stimulation trials. Following the identification of appropriate laser stimulation parameters a silicon probe was inserted in S1. Successful targeting of a whisker barrel was confirmed by manually deflecting whiskers on the mouse's right whisker pad while monitoring S1 spiking activity. The whisker that generated the most S1 activity was then threaded into a glass pipette attached to a piezo actuator. The remaining whiskers were left untouched. While recording neurons in S1, we interleaved trials in which optogenetic activation of ALM (450 trials; 10 Hz square pulse trains for 1.5 s), a tactile stimulus (50 trials; identical to that given in the cross-modal attention task; 0.15 s sinusoidal deflections at 20 Hz, ~600 deg/s), or both the tactile stimulus and the ALM activation was delivered (450 trials). Optogenetic activation of ALM was delivered at each of the three pre-selected amplitudes, either bilaterally, unilaterally to left ALM, or unilaterally to right ALM. ALM stimulation onset occurred 50 ms after tactile stimulus onset in trials where both ALM activation and tactile stimuli were given.

Measurement of body movement. To measure body movements head-fixed mice were placed in a 3D printed tube that was fixed to a cantilever. Movement by the mouse induced forces that caused small displacements (<0.5mm) at the free end. Two photointerruptors (Sharp, GP1S094HCZ0F) were used to convert the vertical and horizontal component of displacements to voltage signals (circuit design and response curve are available in the datasheet of GP1S094HCZ0F). Specifically, the cantilever normally blocks about half of the light passing through, outputting a voltage value in the middle of the range of measurement. Pushing the tube down causes the cantilever to block more light in the vertical sensor and a decrease the output voltage. If less pressure is applied to the tube, this voltage increases. For the horizontal sensor, pushing the tube to the left or right decreases or increases the voltage output, respectively. The voltage was amplified by an op-amp and recorded by the Intan system.

Detecting tongue protrusions. Each video frame was classified as lick or no-lick via a deep convolutional neural network (MATLAB, Deep Learning Toolbox). This network was based on a pretrained network, ResNet-50 (He et al., 2015) but the final layers were redefined to classify the two categories. The training videos recorded a bottom-up view of the mice during optogenetic stimulation. A total of 1611 frames were manually labeled. Image augmentation was performed to expand the training dataset. A standard training scheme was used with a mini-batch size of 32 and a learning rate of 1e-4 to 1e-5. The errors tested on validation data were 1.2% false positive and 1.7% false negative.

S1 activation.

An optic fiber (200-µm diameter, 0.39 NA) coupled to a 473 nm wavelength laser (DHOM-L-473-200mW, UltraLasers) with intensity controlled by an acousto-optic modulator (MTS110-A3-VIS, QuantaTech) was used to deliver direct optogenetic stimulation to left S1 of Emx1;Ai32 mice. Mice were first trained on the cross-modal attention task. Two to three additional days of training were given in which 20% of tactile stimulus trials were replaced with trials where the laser stimulus was given alone but not directed at the skull of the mouse. Photographic masking cloth and tape were used to prevent the mouse from visually detecting the laser stimulus as much as possible. Licking either reward port during these laser stimulus trials was not rewarded. Once it was confirmed that mice were not visually detecting the laser stimulus, ~3 optogenetic-activation sessions and ~3 sham-activation sessions were given in an interleaved manner. During these sessions, the optic fiber was positioned such that its tip was ~2 mm above S1. Optogenetic-activation sessions followed the same procedure as the cross-modal attention task except that 20% of tactile stimulus trials were replaced with trials where direct optogenetic S1 activation (20 Hz sinusoidal wave, 0.15 s, ~3 mW at the tip) was delivered. In sham-activation sessions were identical to optogenetic-activation sessions except that photographic masking tape was used to prevent the laser from impinging on S1.

S1 inhibition.

PV-cre;Ai32 mice implanted with optic-fiber-coupled-microdrives in S1 were trained on the cross-modal attention task. An additional 2-3 training days were given in which laser

stimuli (2-10 mw ramped down to 0 mw over 1.5 s) were delivered that coincided with either the tactile or the visual stimulus (30% of trials) while the laser was decoupled from the implanted optic fiber. Photographic masking cloth and tape were used to prevent the visual detection of the laser stimulus as much as possible. Once it was determined that mice were not reliably responding to the visual detection of the laser stimulus, 3-4 optogenetic-inhibition sessions and 3-4 sham-inhibition sessions were given in an interleaved manner. During optogenetic-inhibition sessions, the laser was coupled to the implanted optic fiber. The trial structure of the sessions was identical to those in the cross-modal attention task except that laser stimuli (2-10 mw ramped down to 0 mw over 1.5 s) were delivered to left S1 in ~25% of tactile and visual stimulus trials. Onset of laser stimulus delivery was either simultaneous with the onset of tactile/visual stimuli or delayed by 50 ms. Additionally, in a subset of trials (~20%), laser stimuli were delivered alone (catch trials). Sham-inhibition sessions were identical to optogenetic-inhibition sessions except that the laser was decoupled from the implanted optic fiber in order to not inhibit S1.

Ideal observer analysis.

Detect probability (DP). The receiver operating characteristic (ROC) analysis was used to calculate the detect and stimulus probability for each neuron. DP was calculated by first binning (25 ms bins unless stated otherwise) the spiking activity for each neuron within tactile/visual stimulus trials (spikes aligned to stimulus onset). Next, trials were grouped by whether the mice either licked a reward port (positive labeled trials) or did not lick a reward port (negative labeled trials) following a tactile/visual stimulus. Within

each time bin a criterion spike rate was systematically varied (using "sklearn .roc_auc_score" in python) such that spike rates falling below criterion were classified as negative trials while those falling above the criterion were classified as positive trials. At each iteration that the criterion was varied, the classification of trials was compared to the true labels to calculate the false positive rate (FPR) and true positive rate (TPR). A ROC curve could then be constructed based on the FPR and TPR at each iteration. The area under the resulting ROC curve (AUC) corresponded to the DP for that time bin and neuron. Bootstrap resampling was used to calculate 95% confidence intervals.

Stimulus probability (SP). SP was calculated using a similar procedure as DP except that positive labeled trials were those in which a tactile/visual stimulus was given, and negative labeled trials were selected as a period before the stimuli were given.

Detect probability onset. DP onset was defined as the first time-bin where DP was significantly different from 0.5 for two consecutive bins after a tactile/visual stimulus.

Modality preference index. Modality preference index is defined by the following equation:

$$\frac{|mean\ tactile\ DP - 0.5| - |mean\ visual\ DP - 0.5|}{|mean\ tactile\ DP - 0.5| + |mean\ visual\ DP - 0.5|}$$

Where the mean tactile and visual DP are defined as the mean DP of the first 500 ms after DP onset.

t-distributed stochastic neighbor embedding (t-SNE) visualization of neuron activity.

Python's "sklearn.manifold.TSNE" was used to construct 2D t-SNE embeddings to group neurons based on activity profiles across trial types. The t-SNE algorithm was fit (perplexity 30; 1400 iterations; learning rate 200, early exaggeration 25) to 1D arrays for each neuron that were constructed by concatenating their normalized spike rates from trials (0-500 s from stimulus onset in 25 ms bins) with the following outcomes: tactile stimulus trials that resulted in a lick, visual stimulus trials that resulted in a lick, tactile stimulus trials that did not result in a lick, and visual stimulus trials that did not result in a lick. The resulting array consisted of 2D coordinates for each neuron.

Quantification and statistical analysis.

We report data as mean ± sem unless otherwise noted. Statistical tests were two-tailed unless otherwise noted. We made no adjustments for multiple comparisons. Prior to using t-tests, we assessed normality using quantile-quantile plots. We chose statistical tests in the following order of decreasing preference (i) parametric tests when appropriate (paired and unpaired t-tests); (ii) Non-parametric tests (sign-test) (ii); randomization tests (permutation and bootstrap). If the tested sample was not symmetrical about its median, we used a sign test.

Unless otherwise noted, confidence intervals were calculated using a nonparametric multistage bootstrap method (Davison & Hinkley, 1997) that simulates the data generation process and incorporates both variability among behavioral sessions for a given mouse as well as variability across mice. The confidence interval for statistic Y (for

example, mean difference between p(lick) for tactile no-manipulation trials and tactile optogenetic inhibition trials) was calculated by first pooling trials across N_k sessions for each of N mice. Next, a set of N primary sampling units (PSU) was obtained by randomly sampling mice with replacement. N_k trials were then randomly sampled with replacement for each PSU. Next, a bootstrap replicate Y* was calculated from the set of PSUs. This process was repeated 10,000 times to obtain a set of Y* bootstrapped replicates. The 95% confidence interval was calculated by taking the 2.5^{th} and 97.5^{th} percentile values of Y*.

We assigned mice of appropriate genotypes to experimental groups arbitrarily, without randomization or blinding. We did not use statistical methods to predetermine sample sizes. Sample sizes are similar to those reported in the field.

Results

We designed a cross-modal attention task for head-fixed mice, in which mice learned to switch between (1) detecting tactile stimuli while ignoring visual stimuli ("tactile block"), and (2) detecting visual stimuli while ignoring tactile stimuli ("visual block"). Mice switched between tactile and visual blocks multiple times per session (Figure 1; 3-5 blocks per session, each containing ~80 trials). Tactile stimuli were comprised of a brief single-whisker deflection (~600 deg/s, sinusoidal waveform; 150 or 50 ms duration) applied to a single whisker on the right side of the face. Visual stimuli were comprised of a brief

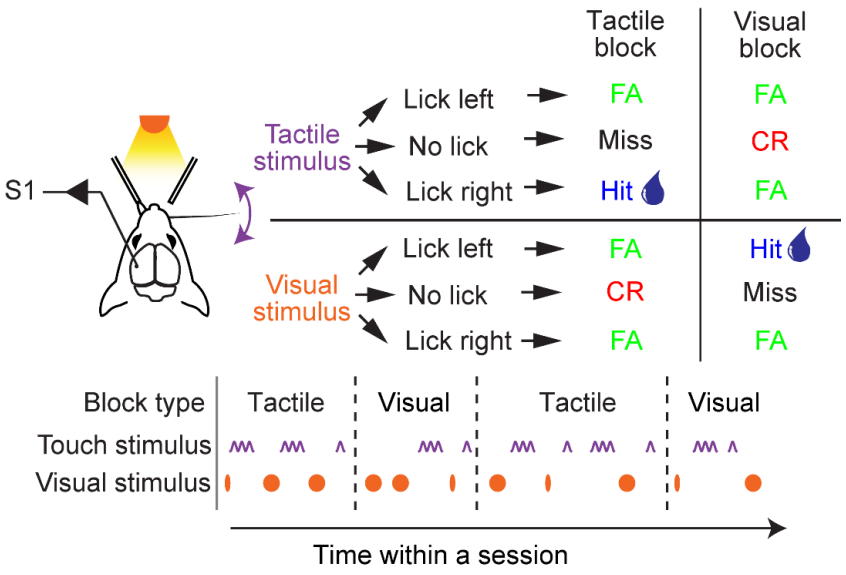

Figure 1. A cross-modal attention task for head-fixed mice.

Tactile (20 Hz sinusoidal single whisker deflection for 150 or 50 ms) and visual stimuli (blue light flash for 150 or 50 ms) were given in a randomly interleaved manner throughout a behavioral session. All stimuli were given during tactile and visual blocks of trials that alternated during a behavioral session (3-5 per session, ~80 trials each). Mice were rewarded with a drop of water for licking to a reward port located to the right of the mouse after a tactile stimulus in a tactile block, or for licking a reward port located to the left of the mouse after a visual stimulus in a visual block.

No reward was given for licking either port after a tactile stimulus in a visual block or after a visual stimulus in a tactile block.

light flash emitted from a point source ($3x10^{-3}$ mW at the tip of a 105 μm, 0.22 NA optical fiber, attenuated with filters; 150 or 50 ms duration; Experimental Procedures) placed in front of the mouse along its midline. Mice were trained to respond to a whisker stimulus occurring in a tactile block by licking to a spout placed to the right of the mouse's midline, and to withhold licking in response to this stimulus during visual blocks. Similarly, mice had to respond to a visual stimulus by licking to a spout placed to the left of the mouse, and to withhold licking in response to visual stimuli during tactile blocks (Figure 1). Correct licking responses to both tactile and visual stimuli ("hits") were rewarded with a drop of water (Figure 1; Experimental Procedures). Correct withholding of responses ("correct rejections") were not rewarded. Trials in which mice failed to respond to tactile stimuli in tactile blocks or visual stimuli in visual blocks were scored as errors ("misses") but not punished. Trials in which mice licked in response to the inappropriate stimulus type, or at the incorrect spout, were scored as error trials ("false alarms") and neither rewarded nor punished. Blocks were not distinguished in any way except for these stimulus-reward contingencies, such that mice had to learn to switch response strategies based on reward availability (if mice failed to switch within ~10 trials, a drop of water was delivered to the rewarded spout; Experimental Procedures).

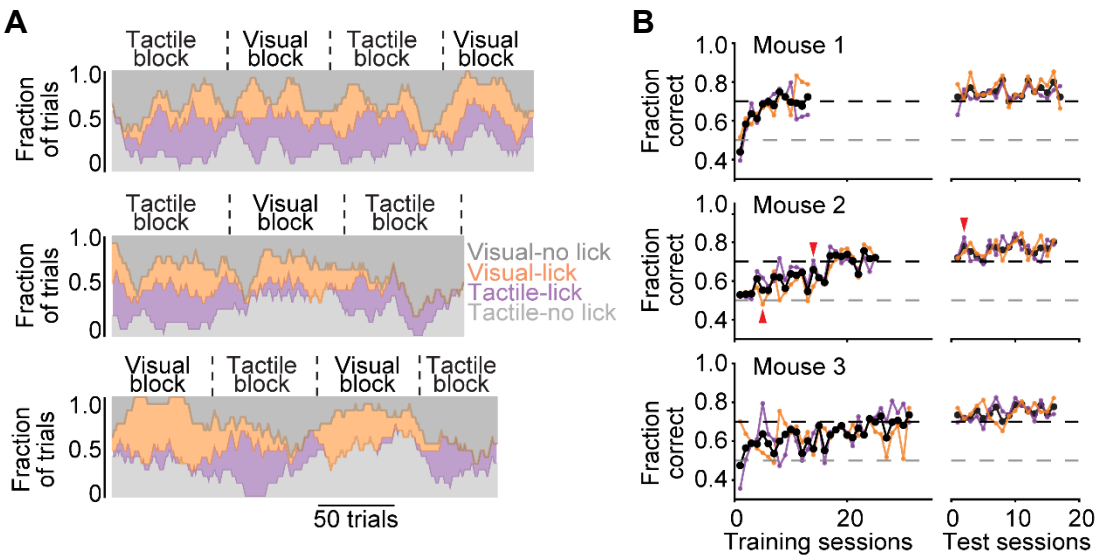

Figure 2. Example performance in cross-modal attention task.

(**A**) Behavioral performance in an early training session (5th session; top), in a session in the middle of training (14th session; middle), and after training (2nd test session; bottom). Horizontal cross-sectional areas indicate the mean fraction of trials (15 trial sliding window, 1 trial step) where tactile stimuli were presented and the mouse licked (purple) or did not lick (light grey), or where visual stimuli were presented and the mouse licked (orange) or did not lick (dark grey). (**B**) Behavioral performance of three example mice during training and testing periods. Overall performance indicated by black traces, performance in tactile blocks given by purple traces, and performance in visual blocks given by orange traces. After training, an additional ~17 test sessions with the same task design where given; test sessions where performance fell below criterion were excluded and not used in later analyses (red arrows mark sessions in (A).

Mice learned to detect stimuli and switch blocks gradually over the course of 2-4 weeks (Figure 2A,B; Figure 3A,B). After training, detection accuracy (fraction of trials correct) was similar for both tactile and visual blocks (Figure 3B,C; tactile block: 73% correct; visual block: 75% correct). Reaction times were slightly but significantly shorter for tactile stimuli (Figure 3D; 397 ± 224 vs 521 ± 252 ms; median ± interquartile range [IQR]). Head-fixed mice can therefore flexibly switch between detecting either tactile or visual stimuli, while rejecting distractors of the other type.

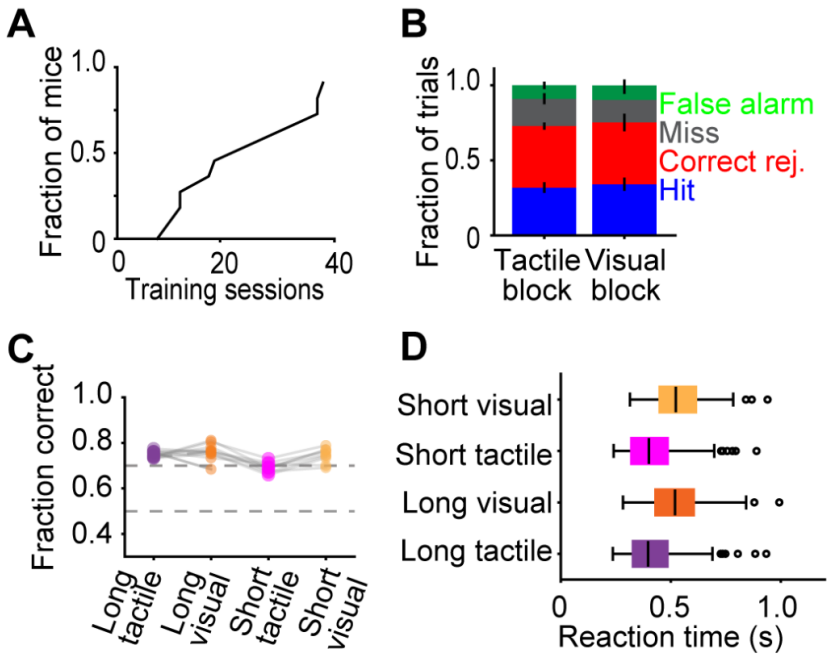

Figure 3 Cross-modal attention task performance across mice.

(**A**) Time to criterion performance across mice (median 19). (**B**) The fraction of trial outcomes was similar across tactile and visual blocks. Error bars indicate ± sem. (**C**) Performance was similar across all stimulus types for all mice. (**D**) Reaction time distributions across the different stimulus types. Black vertical lines indicate medians, boxes indicate interquartile range (IQR), whiskers indicate 1.5 x IQR, circles indicate outliers. n = 11 for A-D.

Sensory and motor activity combine in S1

To examine S1 activity during task performance, we obtained single-unit recordings from S1 using 32-channel tetrode microdrives, targeted based on responsiveness to the stimulated whisker (Figure 4A; Experimental Procedures).

During tactile blocks, in which mice had to lick in response to whisker stimuli, S1 activity on hit trials was on average larger than on miss trials (Figure 4B,C). Neural responses to the whisker stimulus were evident in both hits and misses, indicating that S1 neurons responded to the whisker stimulus per se, as expected. However, mean activity on hit but not miss trials remained elevated until the reaction time or later (Figure 4B,C). This is consistent with the observation of enhanced hit vs miss responses in prior work using simple tactile detection tasks (Kwon et al., 2016; Le Merre et al., 2018; Sachidhanandam et al., 2013; Takahashi et al., 2016; Yamashita and Petersen, 2016; Yang et al., 2016). On false alarm trials, mean activity also exceeded baseline prior to licks (Figure 4B,C),. On correct rejection trials, in which visual stimuli were presented but mice successfully made no response, activity did not exceed baseline (Figure 4B,C), indicating that there was no visual response per se in S1. During visual blocks, we also observed no obvious response during the visual stimuli, but responses to the whisker stimulus were evident (correct rejections; Figure 4B,C). On hit and false alarm but not miss trials (i.e. on trials with licks), mean activity was elevated for hundreds of milliseconds prior to the lick.

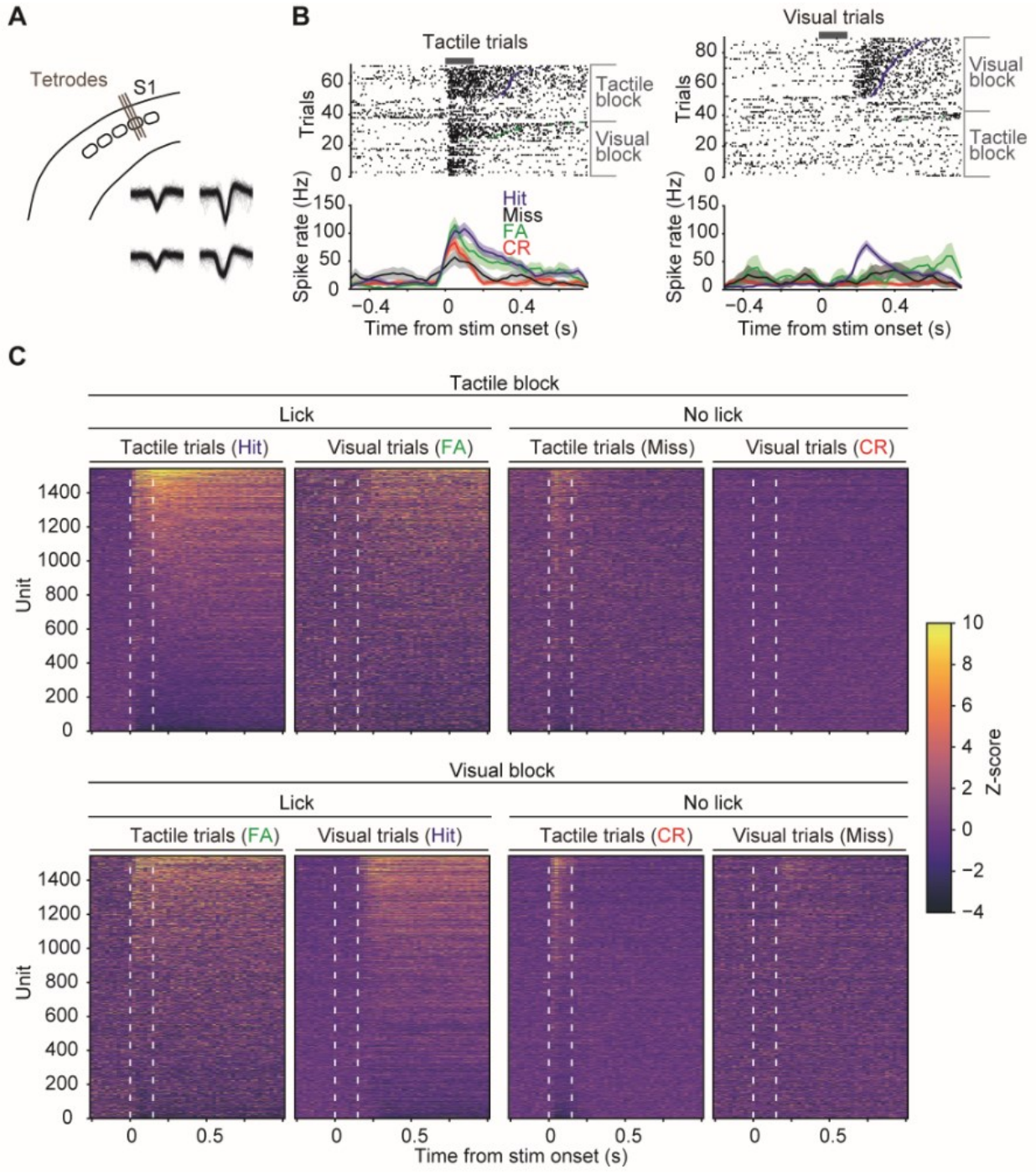

Figure 4. Tactile responses and motor-related activity in S1.

(**A**) Extracellular single-unit activity was recorded in whisker S1 (barrel) cortex using 32-channel tetrode microdrives. (**B**) Raster plots (top) and peristimulus spike time histograms (PSTHs, bottom; 25 ms bins, mean ± sem) for an example unit. Rasters and PSTHs are aligned to the onset of either

the long tactile stimuli (left, “tactile trials”) or the long visual stimuli (right, “visual trials”) and sorted by block and trial outcome. Thick black bars indicate period of stimulus delivery. (**C**) Normalized activity across the population of recorded neurons (n = 1550 units from 9 mice). Trials are grouped by block type, stimulus type, trial outcome and sorted by mean activity during a 500 ms window after stimulus onset in tactile Hit trials. White dashed lines indicate the onset and offset the long tactile or visual stimuli.

Together, these results show that spiking of neurons in S1 during the cross-modal attention task reflected tactile but not visual sensory-evoked responses, as well as motor-related activity associated with the licking behavioral responses.

We next examined in more detail how the activity of S1 neurons related to the stimulus and to the licking response. S1 activity was clearly modulated by the stimulus condition (tactile or visual) and by the response of the mouse (lick or no lick; Figure 4). Our task design included both long (150 ms) and short (50 ms) duration tactile and visual stimuli. We therefore grouped trials into 8 types (4 stimulus conditions X 2 possible responses) and examined the mean spiking responses for each type. As expected, long tactile stimuli evoked a more protracted evoked response during the first 150 ms after stimulus onset (Figure 5A,B). This reflects simply the tactile responsiveness of S1 neurons. Similarly expected, activity was identical for both long and short visual stimuli, reflecting the lack of visual responsiveness of S1 neurons in our task (Figure 5A,B).

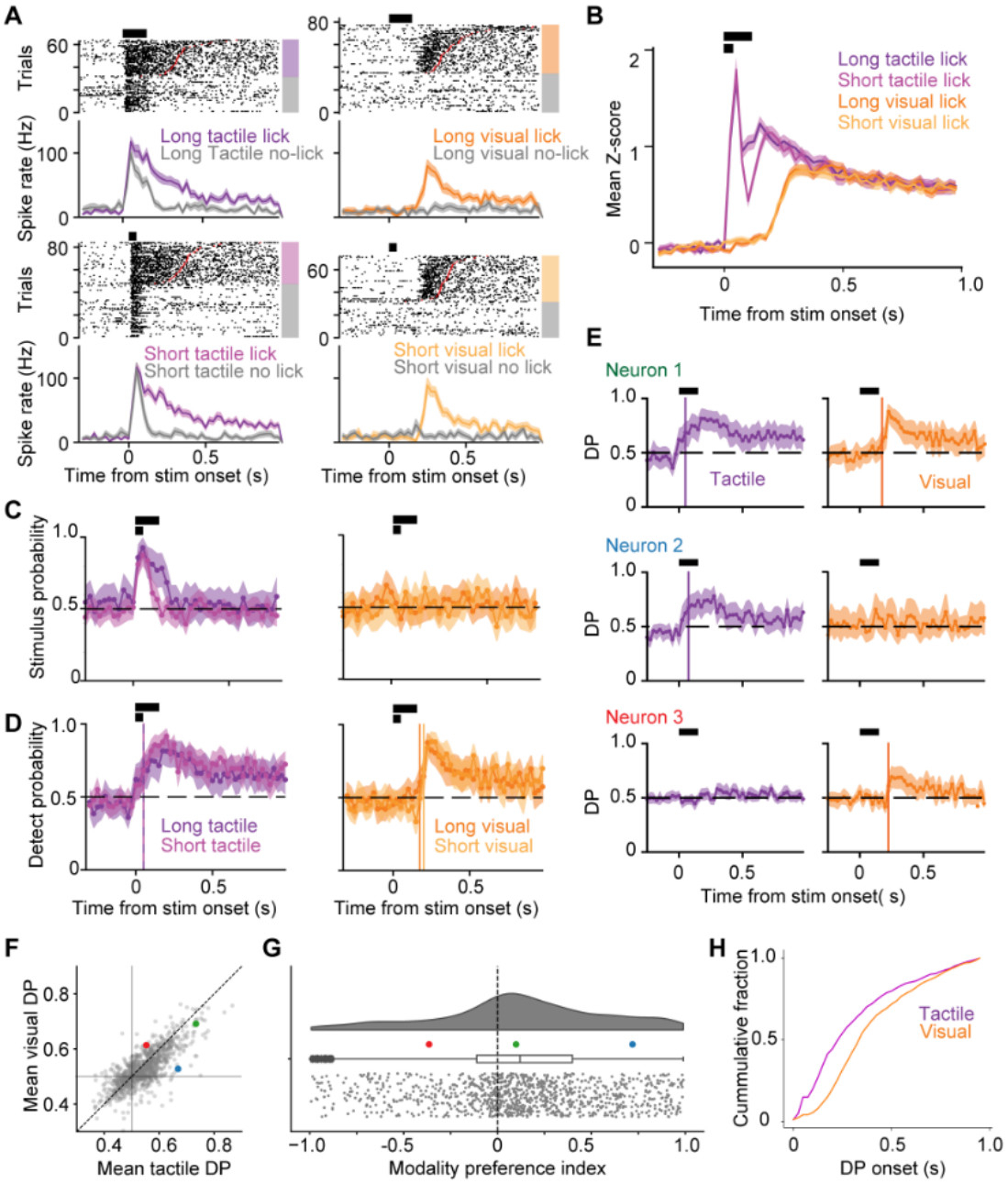

Figure 5. Trial-by-trial encoding of tactile stimuli and lick responses.

(**A**) Raster plots and PSTHs (mean ± sem, 25 ms bins) for an example neuron separately for long (150 ms; top row) and short (50 ms; bottom row) tactile (left column) and visual (right column) stimuli. Trials are grouped within each raster and PSTH by whether or not the mouse licked. Increased activity is evident in association with the tactile stimulus, licking after the tactile stimulus, licking after the visual stimulus, but not the visual stimulus itself. (**B**) Mean normalized activity (± sem, 25 ms bins) of all neurons recorded (n = 1550) across stimulus trials where the mouse made a licking response. Horizontal black bars indicate period of short and long stimulus

delivery. (**C**) Stimulus probability (SP; an ideal-observer measure of ability to decode stimulus) for the example neuron in (A) (mean ± 95% confidence interval [CI], 25 ms bins). Significant (>0.5) SP was prolonged for long (dark purple) relative to short (light purple) tactile stimulus trials, and not evident for either long (dark orange) or short (light orange) visual stimulus trials. (**D**) Detect probability (DP; ideal-observer measure of ability to decode whether mouse detected stimulus) for the example neuron in (A) (mean ± 95% CI, 25 ms bins). Significant DP was detected for long and short tactile and visual stimulus trials. Vertical colored lines indicate onset of significant DP for the different trial types (Experimental Procedures). (**E**) Three example neurons illustrating the range of DP responses. Neurons could show significant DP for both tactile and visual trials (top), for only tactile lick trials (middle), or for only visual trials (bottom). (F) Scatter plot comparing the mean tactile and visual DP values for each unit (limited to those units with significant DP for both trial types; values show means over first 500 ms after DP onset). Colored symbols indicate example neurons in (E). (G) Scatter plot and distribution of modality preference index (MPI; Experimental Procedures) for units with a significant DP in both trial types. Boxplot indicates median, IQR, and 1.5 x IQR (whiskers) of MPI. (H) Cumulative distribution of the time of DP onset with respect to stimulus onset for tactile (purple) and visual (orange) trials.

We used ideal-observer analysis to quantify how well the single-trial activity of individual neurons could be used to discriminate the presence of the stimulus ("stimulus probability", SP), or predict the response of the mouse ("detect probability", DP; Experimental Procedures). S1 neurons robustly signaled the presence of tactile stimuli on a trial-by-trial basis, but not the presence of visual stimuli (Figure 5C; SP > 0.5). Individual S1 neurons could also predict the licking response of the mouse (Figure 5D; DP > 0.5).

Prediction of the licking response was similar for short and long stimuli of a given modality (Figure 5D). This is consistent with decision-related activity reflecting top-down feedback rather than feed-forward stimulus responses (Nienborg and Cumming, 2009; Yang et al., 2016).

A given neuron could predict the licking response of the mouse for both tactile (right-side) and visual (left-side) licks, or at the extremes for only tactile or only visual licks (Figure 5E). Most neurons, however, predicted licking to both sides to some degree, with an overall slight bias to better predict tactile stimulus responses (Figure 5F,G).

DP onsets occurred earlier for tactile compared with visual detection trials (Figure 5D,E). This could not be explained simply by trial-by-trial reaction times (Figure 6). Thus, while S1 neurons predicted licking in response to both tactile and visual stimuli, they did so earlier for tactile stimuli. Together, these results show that S1 activity in our task has a unimodal sensory component that reflects tactile responsiveness, and a motor component that reflects lick direction.

To assess how stimulus- and motor-related activity was distributed across the population of neurons and across time, we visualized the spatial and temporal distribution of SP and DP superimposed on a depiction of neurons grouped by similarity of activity pattern (using t-SNE dimensionality reduction; Experimental Procedures; Figure 7A,B). The populations of neurons showing positive-going (> 0.5) SP and DP partially overlapped, as did populations showing negative-going (<0.5) SP and DP (Figure 7A,B). A small fraction of neurons showed SP and DP simultaneously within individual 50 ms time bins (1.4% of neurons; higher than chance expectation of 0.4% based on independent SP and DP). Simultaneous SP and DP occurred in a time period prior to the typical reaction time (Figure 7A,B). Thus, sensory and motor activity combined in individual neurons during the decision-relevant period.

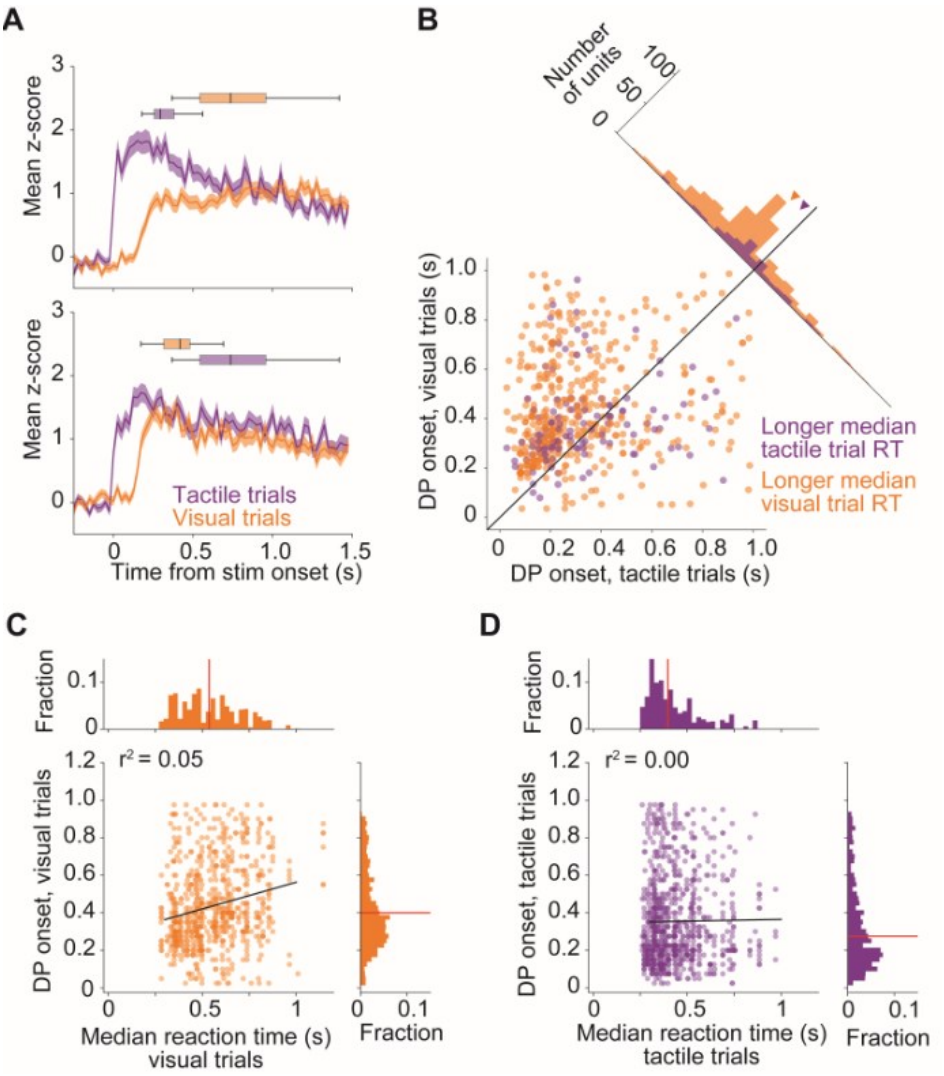

Figure 6. Detect probability onset timing differences between tactile and visual detection are not explained by reaction times.

(**A**) Recording sessions were grouped into terciles based on each session's median reaction time, separately for tactile and visual reaction times. Top, mean z-scored activity for tactile and visual trials, where the tactile trials came from the first (fastest) tercile group and the visual trials from the third (slowest) tercile group. Reaction time distributions are indicated by horizontal boxplots (median, IQR; whiskers: 1.5 X IQR). Bottom, similar to top panel but comparing tactile trials from third (slowest reaction times) tercile vs visual trials from first (fastest) tercile. (**B**) Scatter plot and corresponding histogram comparing DP onsets for tactile and visual trials for each neuron grouped by whether neurons were recorded in sessions where the medial tactile (purple) or median visual (orange) reaction time was longer. (**C**) Scatter plot of DP onsets in visual trials as a function of the corresponding median visual trial reaction times for the corresponding session. (**D**) Same as (C) but for tactile trial DP onsets and tactile trial reaction times.

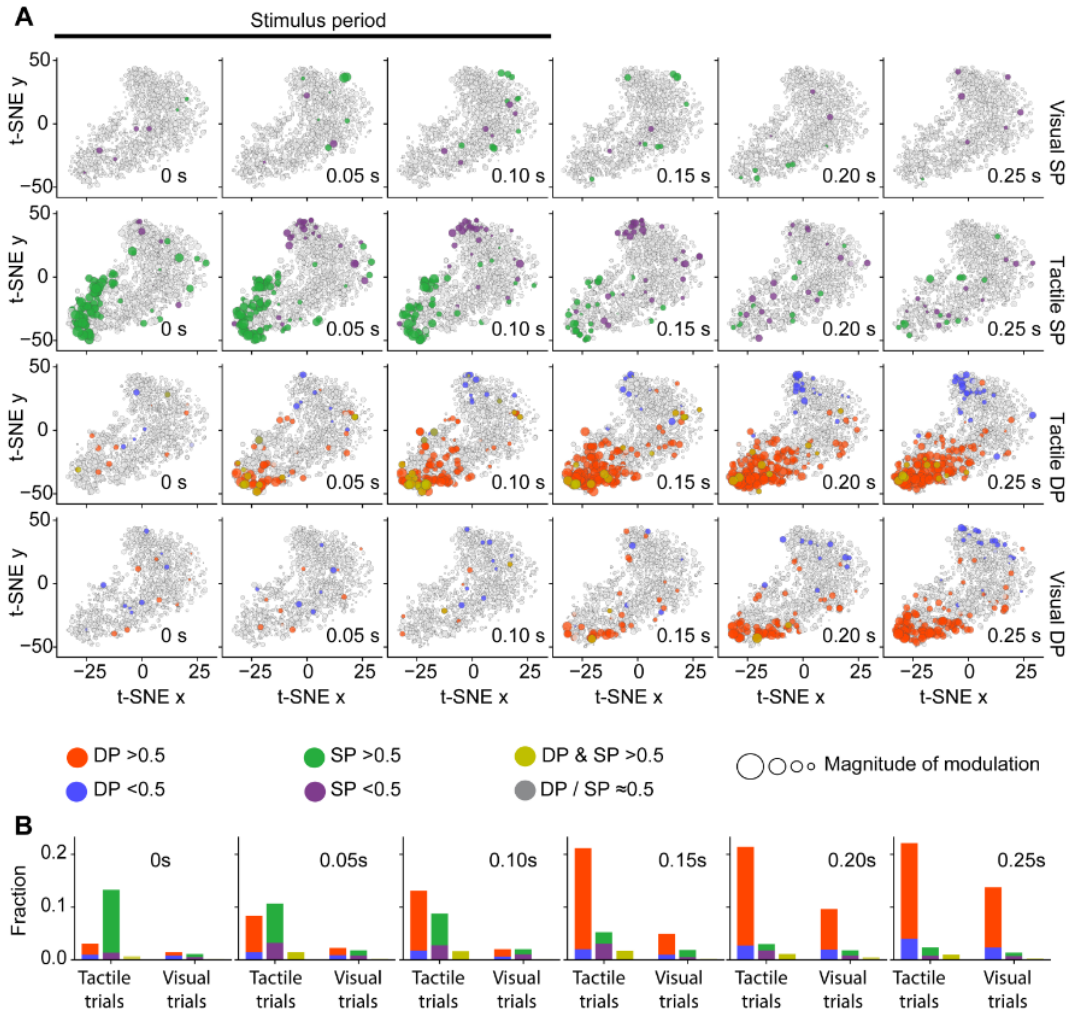

Figure 7. Sensory and motor activity is encoded in partially overlapping subsets of neurons.

(**A**) Time course of SP and DP across the population of neurons (n = 1550), depicted after grouping neurons by similarity of activity profiles (t-SNE 2D embedding; Experimental Procedures). In tactile trials, significant SP (second row; green, purple markers) overlapped with significant DP (third row; red, blue markers) in time and in a subset of neurons (yellow markers; third row). In visual trials, very few neurons showed significant SP (first row; green, purple markers) and showed delayed DP onset (bottom row, red, blue markers) relative to tactile trials. (**B**) Fraction of all neurons (n = 1550) that showed significant SP and DP across time after stimulus onset. Panel A inspired by (Chen et al., 2017).

We identified for further analysis neurons that showed significant values of both SP and DP at any time point within the first 1 s following the time of stimulus onset (Figure 8A) (corresponding to the longest reaction times; Figure 3D). We focused on these neurons to quantify motor activity (i.e. DP) among stimulus-encoding neurons, which presumably are relevant to the perceptual decision. DP in this subset of neurons (Figure 8A) had an earlier onset and was stronger (Figure 8B). This suggests that a subset of stimulus-encoding S1 neurons combines excitation from sensory and motor sources such that spike rate is enhanced during the period of stimulus presentation and response.

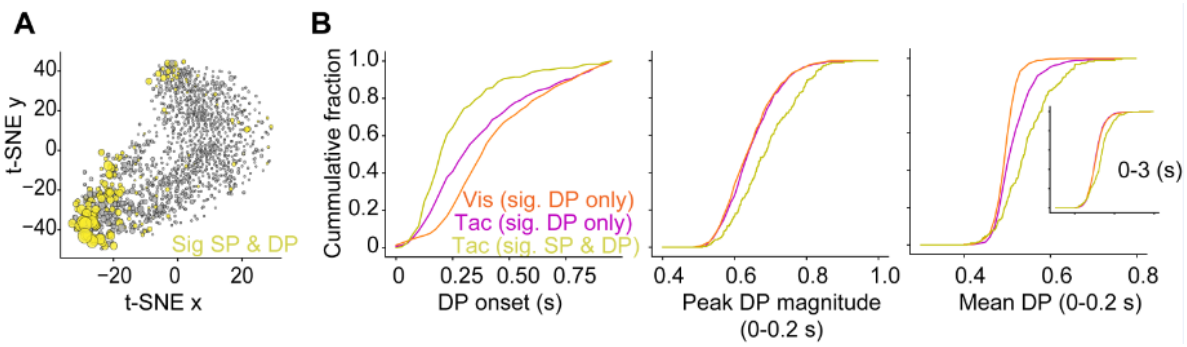

Figure 8. Sensory and motor activity combine to enhance spike rate in a subset of neurons.

(**A**) Neurons that showed both positive-going (>0.5) SP and positive-going DP at any point in tactile trials are colored yellow (symbols are sized to depict the product of SP and DP). (**B**) Left, cumulative histogram of DP onset with respect to the time of stimulus onset. Middle, peak DP during the first 200 ms after stimulus onset. Right, mean DP during the first 200 ms (right), and mean DP during the duration of a trial (inset). Yellow histograms indicate neurons in (A). Purple and orange histograms show neurons with significant DP in touch (not including neurons in A) and visual trials, respectively.

We found that neurons in S1 responded to tactile stimuli, as expected, and to licking-related movements in response to either tactile or visual stimuli. Moreover, licking-

related activity occurred earlier and was on average greater for tactile licking. However, in the experiments presented thus far the direction of licking was confounded with the stimulus modality. Specifically, mice licked to the right in response to tactile stimuli, and to the left in response to visual stimuli. To determine whether licking-related activity in S1 was due strictly to the direction of licking, we modified the task to include two new block types: one in which mice licked to the left in response to tactile stimuli (but without visual distractors), and one in which mice licked to the right in response to visual stimuli (but without tactile distractors; Figure 9A; "direction reversal task"). In each session, mice therefore licked either to the right or to the left in response to tactile stimuli (in different blocks) and licked either to the left or to the right in response to visual stimuli (in different blocks). We recorded from whisker S1 in these mice during task performance (3 mice trained de novo on this task, and 1 mouse retrained on this task after performing the task depicted in Figure 1).

Remarkably, activity in touch-lick-right trials was greater than in touch-lick-left trials following the onset of the stimulus (Figure 9B,C), despite similar task performance for the two block types (Figure 10). In contrast, activity was similar for both visual-lick-right and visual-lick-left trials (Figure 9B,C). We used ideal observer analysis to quantify

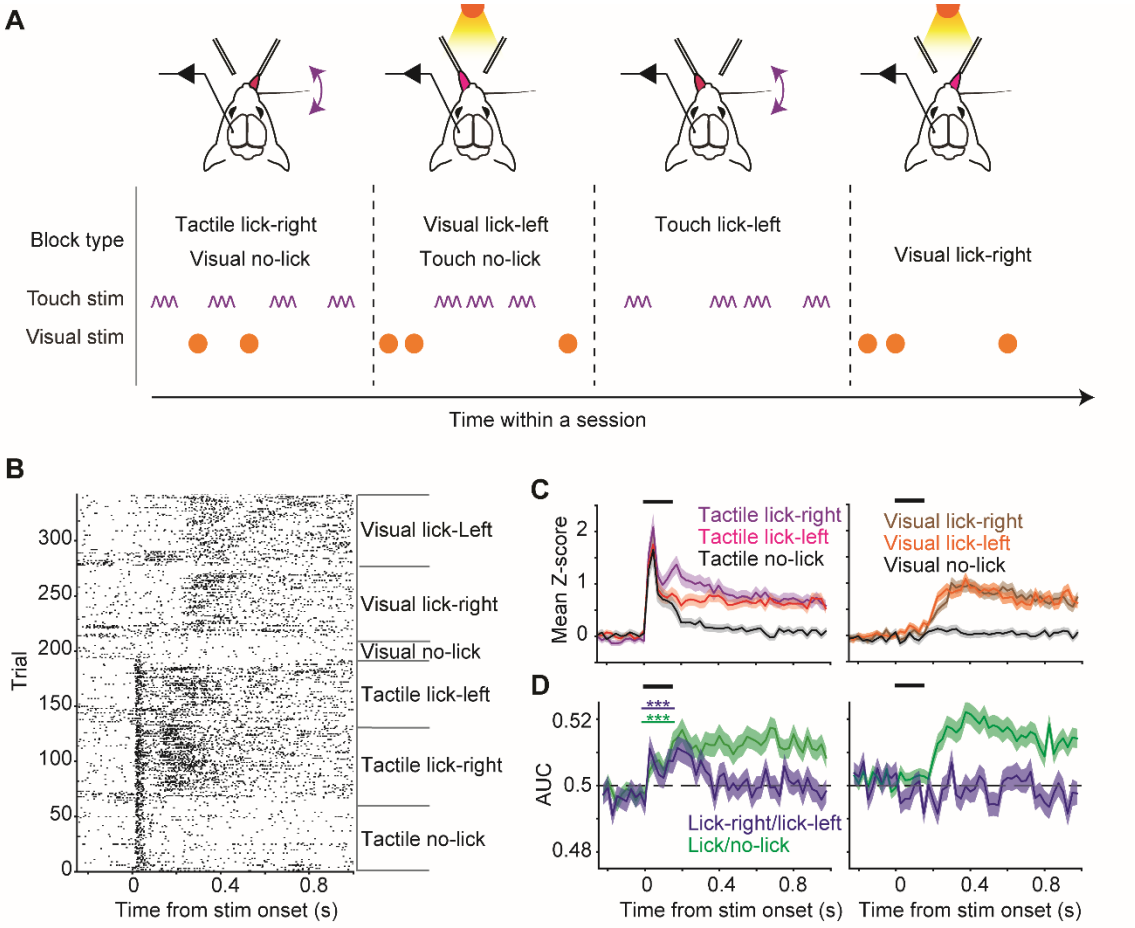

Figure 9. Sensory-motor integration in S1

(**A**) Cross-modal attention task with added blocks of trials to control for lick direction. Two additional block types were added to test sessions for mice trained on the cross-modal attention task, one in which where mice were given only tactile trials and rewarded for licking left ("tactile lick-left" blocks) or were given only visual trials and rewarded for licking right ("visual lick-right" blocks). (**B**) Raster plot for an example neuron sorted by stimulus type and trial outcome. (**C**) Mean normalized PSTHs for tactile (left) and visual (right) trials, grouped by lick outcome (no-lick, lick-left or lick-right). (**D**) Left, mean AUC (area under the receiver-operating curve, ± sem) for an ideal observer discriminating tactile lick vs no-lick trials (green traces, $P < 1 \times 10^{-3}$, one-sided one-sample t-test on first 150 ms bin, n = 375 neurons) or lick-right vs lick-left trials (blue traces, $P < 1 \times 10^{-3}$). Right, same as at right but for visual trials.

how well individual neurons discriminated: (1) the presence vs absence of licking, and (2) the lick direction. Neurons encoded the presence vs absence of licking for both visual and

tactile stimuli (Figure 9D, green curves). However, for tactile but not visual stimuli, individual neurons also encoded lick direction for hundreds of milliseconds following stimulus onset (Figure 9D, blue curves; Figure 10). Thus, single neurons in whisker S1 encoded the direction of licking in response to tactile but not visual stimuli. Because they did not discriminate left vs right licking following visual stimuli, they did not encode lick direction per se. Rather, S1 neurons integrated sensory and motor activity.

A limitation of the direction reversal task is that the tactile-lick-left blocks did not have distractors (Figure 9A), and therefore the enhanced activity we observed on tactile-lick-right vs touch-lick-left trials (Figure 9C) could be due to differences in difficulty or attentional demands between the two block types rather than to sensory-motor integration. We therefore compared mice trained in the normal task (of Figure 1; "tactile-lick-right" mice) with mice trained in the same task but with opposite contingencies ("tactile-lick-left" mice), such that detection of tactile stimuli was reported by licking to the left, and visual stimuli by licking to the right (Figure 11). Mice trained in the tactile-lick-right version showed a greater DP for touch compared with touch-lick-left mice (Figure 11). Thus, consistent with results from the direction reversal task , sensory-motor activity was enhanced for contraversive licking in response to tactile stimuli.

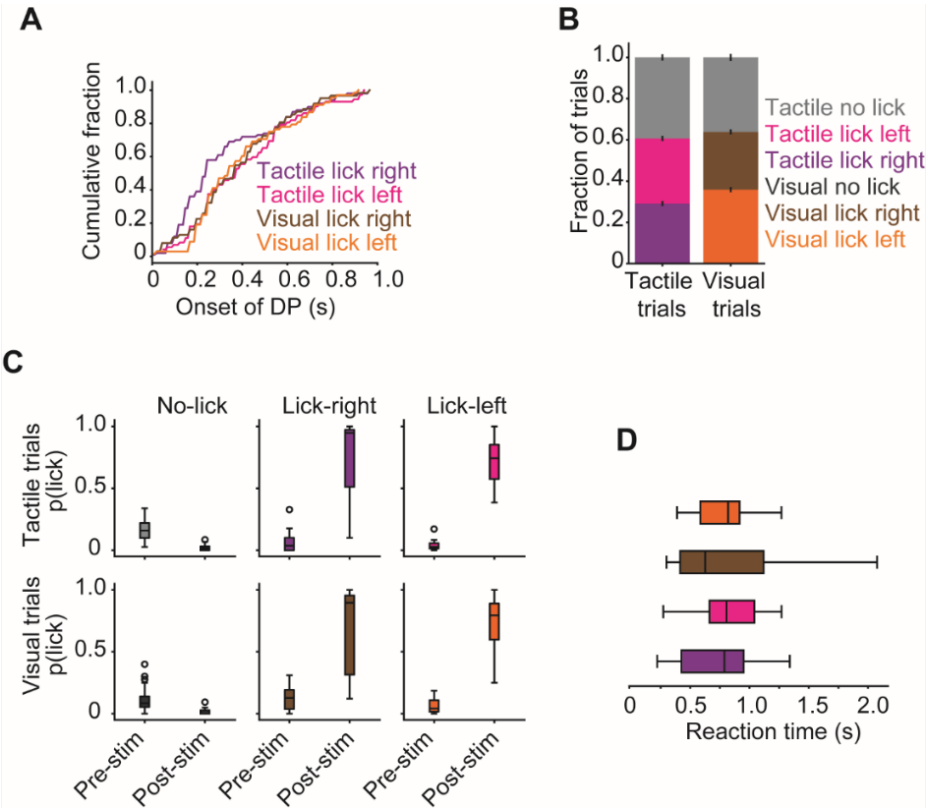

Figure 10. Performance for mice trained in cross-modal task with additional block types.

(**A**) Cumulative histogram of DP onset times for different trial types from neurons recorded during the modified cross-modal attention task. (**B**) Fractions of different trial outcomes for tactile and visual trials (error bars: ± sem; n = 28 sessions). (**C**) Distributions across sessions of the probability of each possible lick outcome, separately for post-stimulus and pre-stimulus periods. (**D**) Distributions of reaction times for the different trial types. (**C**-**D**) Boxes indicate median and IQR; whiskers indicate 1.5 x IQR; fliers indicate values greater than 1.5 x IQR.

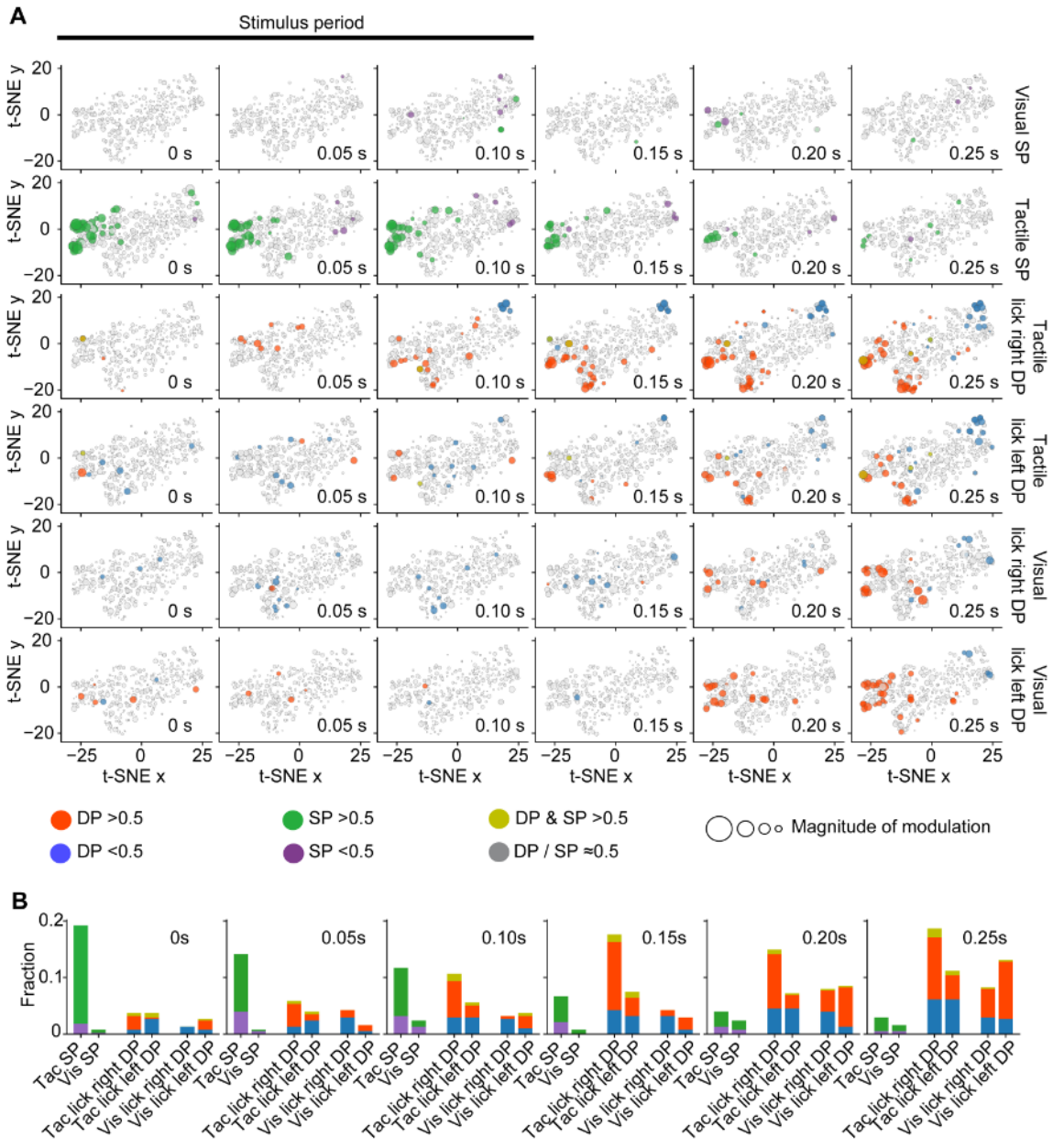

Figure 11. Sensory-motor interactions are enhanced for contraversive licking to the tactile stimulus.

(**A**) Time course of SP and DP across the population of neurons (n = 375), depicted after grouping neurons by similarity of activity profiles (t-SNE 2D embedding; Experimental Procedures). In tactile lick-right trials, significant SP (second row; green, purple markers) overlapped with significant DP (third row; red, blue markers) in time and in a subset of neurons (yellow markers; third row). In tactile lick-left trials (fourth row; red, blue markers) DP onset was delayed in time relative to tactile lick-right trials. In visual trials, very few neurons showed significant SP (first

row; green, purple markers) and showed similar DP onset in both lick-right (fifth row; red, blue markers) and lick-left trials (bottom row; red, blue markers) relative to tactile trials. (**B**) Fraction of all neurons that showed significant SP and DP across time after stimulus onset.

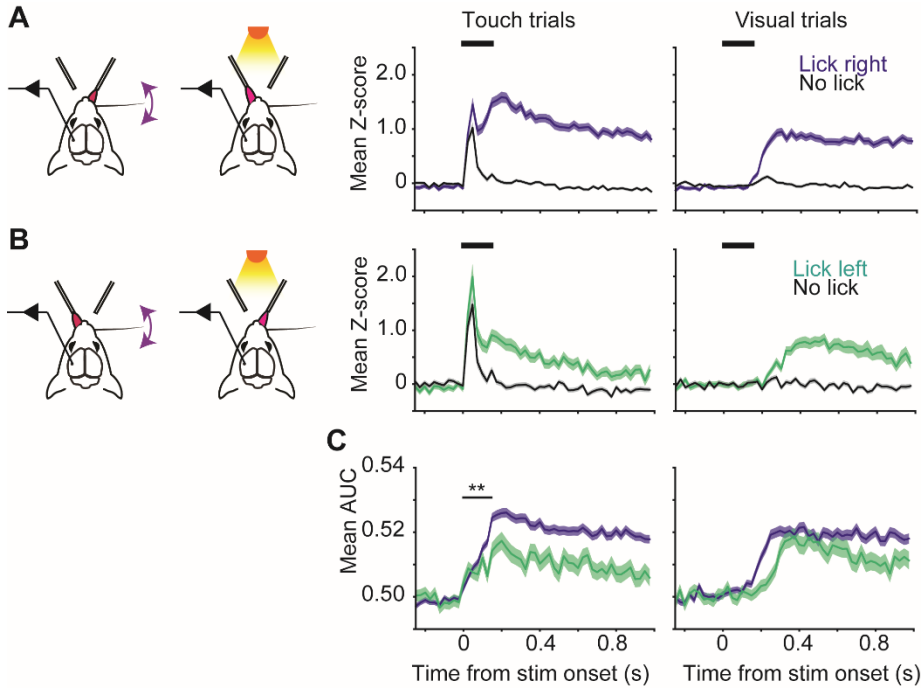

Figure 12. Greater motor-related activity in mice trained on tactile-lick-right vs mice trained on tactile-lick-left.

(**A**) Task design and mean z-scored activity of neurons recorded in mice (n = 9) trained in the cross-modal attention task with the original stimulus-lick direction contingency (tactile-lick-right; visual-lick-left). (**B**) Same as (A) but for mice (n = 4) trained in the cross-modal attention task with reverse stimulus-lick direction contingencies (tactile-lick-left; visual-lick-right). (**C**) Left, mean AUC (± sem) for an ideal observer discriminating tactile lick-right vs no-lick trials (purple) or discriminating lick-left vs no-lick trials (green). Right, same as at right but for visual trials. Blue and green curves are significantly different in the first 150 ms window after stimulus onset ($p = 1 \times 10^{-2}$, two-sided t-test).

Premotor circuit activation mimics task activity in S1

Whisker S1 showed both tactile sensory responses and activity associated with the operantly conditioned licking movements. To test whether licking motor circuits could generate such motor-related activity in whisker S1, we combined single-unit recordings from S1 using 64-channel silicon probe arrays with optogenetic stimulation of tongue premotor cortex (the anterior lateral motor cortex, ALM (Chen et al., 2017; Guo et al., 2014; Komiyama et al., 2010; Li et al., 2015)) in naïve Emx1-Cre;Ai32 mice (Figure 12). We monitored movements of the tongue and jaw using high-speed video, and used a sensor of stresses exerted by the mouse on the tube in which it sat to detect other movements (Experimental Procedures). Mice were awake but completely untrained in the task. We delivered ALM stimulation either alone or paired with the whisker stimuli used in the task. We titrated ALM stimulation such that high intensities evoked tongue movements (Allen et al., 2017; Komiyama et al., 2010; Li, et al., 2015), but at low intensities overt (out of mouth) tongue movements were not evident (Figure 12B).

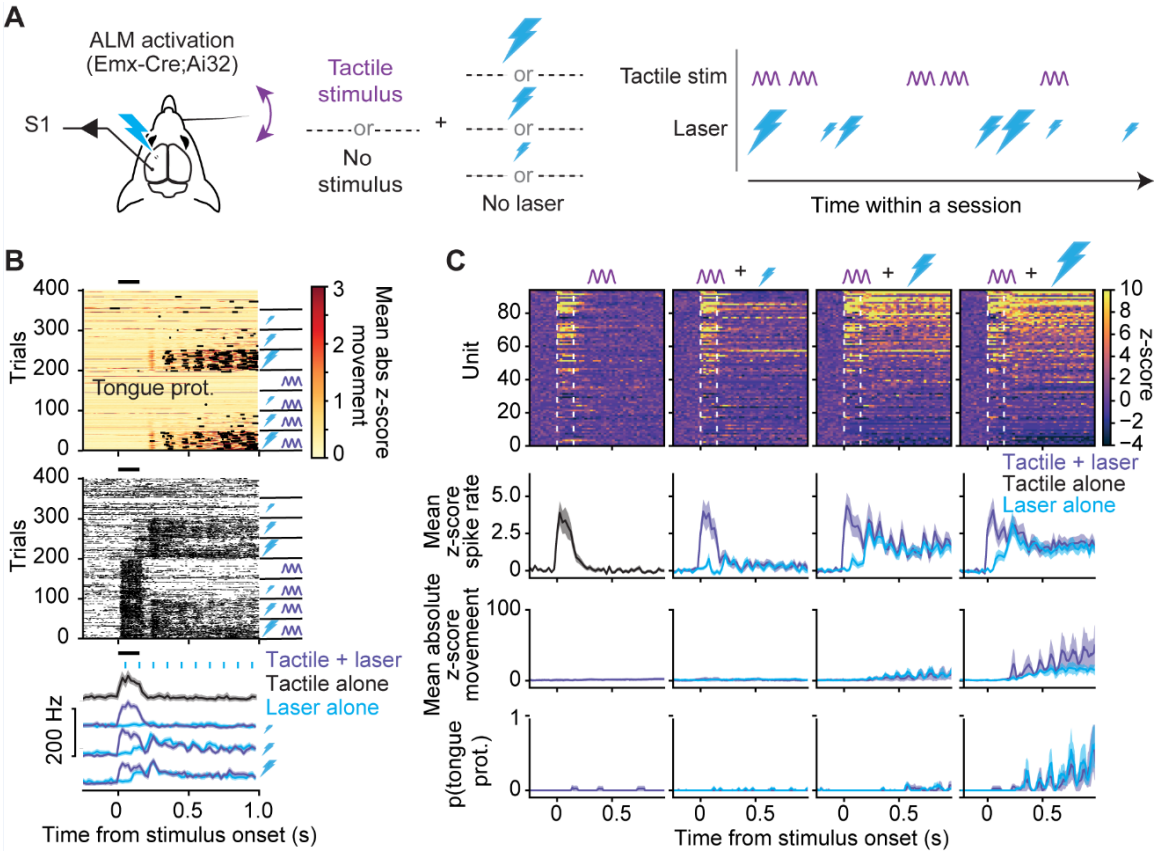

Figure 13. Tongue premotor cortex stimulation mimics task activity in S1.

(**A**) Schematic of experiment depicting optogenetic activation of ALM with or without tactile stimulation, while recording whisker S1 neurons in naïve mice. Three levels of laser intensity were presented alone or paired with a tactile stimulus (20 Hz sinusoidal single whisker deflection for 150 ms). (**B**) Top, tongue protrusions (horizontal black bars; obtained via high-speed video) superimposed on a heatmap showing normalized signal from a sensor that detected movements of the mouse (Experimental Procedures). Trials are sorted according to optogenetic and whisker stimulation conditions, as indicated by blue bolts and tactile stimulus icons in right-most column before color bar. Middle, raster plot of an example neuron during the different optogenetic and tactile stimulus presentation trials. Bottom, PSTHs (mean ± sem) for the same example neuron for each stimulation condition. (**C**) Heatmaps (top row) showing mean z-scored response for each neuron (n = 97 from 3 mice) to whisker stimulation alone (left column) or in combination with optogenetic excitation of ALM at increasing intensities (right three columns), and the corresponding z-scored PSTHs (second row). Comparing neural activity with mean normalized movement (third row; ± sem) and the probability of tongue protrusions (bottom row; ± sem) show

that ALM excitation evokes S1 activity even at levels that evoke negligible movements (cf. second column from left).

Whisker stimulation alone evoked activity that decayed to baseline shortly after stimulus offset (Figure 12B, bottom and Figure 12C, left column), similar to activity on correct rejections during the task (cf. Figure 12C vs Figure 4). However, ALM stimulation (alone or when paired with the whisker stimulus) evoked activity in S1 that mimicked task-related motor signals (Figure 12B,C) (Allen et al., 2017). This occurred even at intensities too low to evoke tongue movements detectable with our high-speed video, and before the onset of movements detectable with our stress sensor (Figure 12C). Thus, motor-related signals we observed in S1 during task performance could be mimicked by activation of the premotor circuitry likely responsible for the directional licking (Guo et al., 2014; Li et al., 2015) that served as the final output of the sensory-motor transformations required by our task.

S1 activity is read out in a context-specific manner

We observed sensory-motor activity in S1 during task performance, including activity that was enhanced during tactile blocks and predicted detection. To test whether S1 activity promotes detection in a context-specific manner we trained new Emx1-Cre;Ai32 mice in the cross-modal task. During task performance, we introduced a small

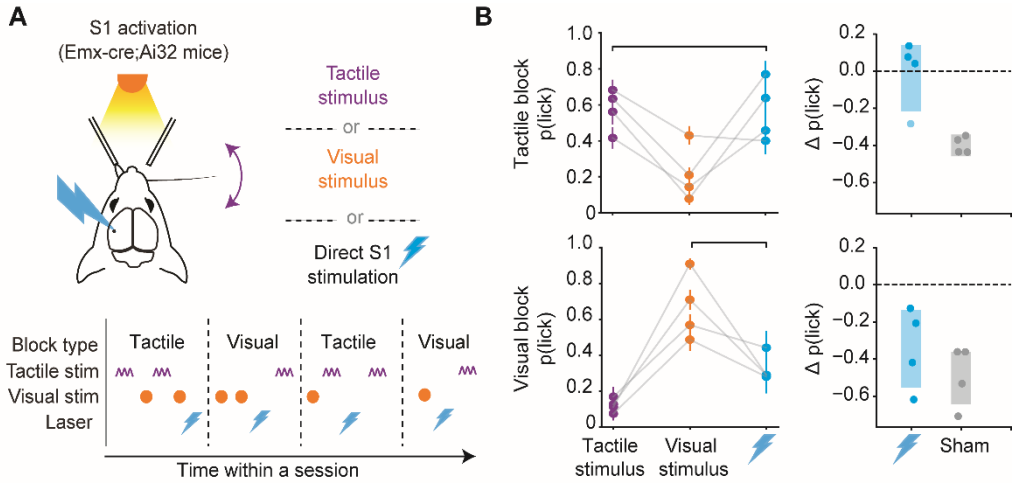

Figure 14. S1 stimulation promotes lick responses during tactile but not visual blocks.

(**A**) Schematic of experiment. In 20% of test-session trials, direct optogenetic activation of S1 replaced either tactile or visual stimuli in mice trained on the cross-modal attention task. (**B**) Probability that mice licked in each trial type during tactile (top) and visual (bottom) blocks. (**C**) Top, quantification of the difference in p(lick) after direct optogenetic excitation of S1 vs after tactile stimuli in tactile blocks (data indicated by bracket from (B)) for 4 mice. Sham trials are taken from days in which mice underwent the same experiment as in (A) but with laser illumination of S1 obstructed. Bottom, similar to top panel but comparing p(lick) after direct optogenetic excitation of S1 vs after visual stimuli in visual blocks. Shaded regions indicate 95% CI for the mean Δ p(lick). Excitation of S1 elicited licking at comparable levels to tactile stimuli in tactile blocks but did not elicit licking at comparable levels to visual stimuli in visual blocks.

fraction (20%) of trials in both tactile and visual blocks in which S1 excitatory neurons were optogenetically excited in place of a sensory stimulus (Figure 13A). During tactile

blocks, optogenetic excitation increased the lick rate of the mice to levels comparable to tactile stimulation (Figure 13B). Excitation during visual blocks, in contrast, did not produce lick rates comparable to visual stimulation (Figure 13B). Optogenetic excitation of S1 therefore promoted lick responses specifically during touch but not visual blocks. Thus, activity in S1 impacts detection in a context-specific manner.

To further assay the role of S1 activity in the cross-modal task, we performed experiments in which we optogenetically inhibited S1 via excitation of parvalbumin-positive GABAergic neurons in PV-Cre;Ai32 mice (Figure 14). On a small fraction (30%) of trials we inhibited S1 in a 1.5 s time window beginning either simultaneous with, or delayed by 50 ms with respect to, the onset of the tactile or visual stimulus (Figure 14A). These two inhibition onset latencies allowed us to reduce S1 activity during either a period ranging from stimulus onset to typical reaction times, or (for the 50 ms delay condition), beginning after the initial sensory response but capturing the later sensory-motor activity (see also: (Sachidhanandam et al., 2013)). Tetrode recordings from S1 during a subset of these experiments (Experimental Procedures) showed that, as expected, optogenetic stimulation in PV-Cre;Ai32 mice inhibited the majority of neurons (Figure 14B,C), but strongly excited a small number of presumably GABAergic neurons (Figure 14C). These recordings also showed that delayed inhibition left intact the early tactile response, whereas simultaneous inhibition did not (Figure 14B,C).

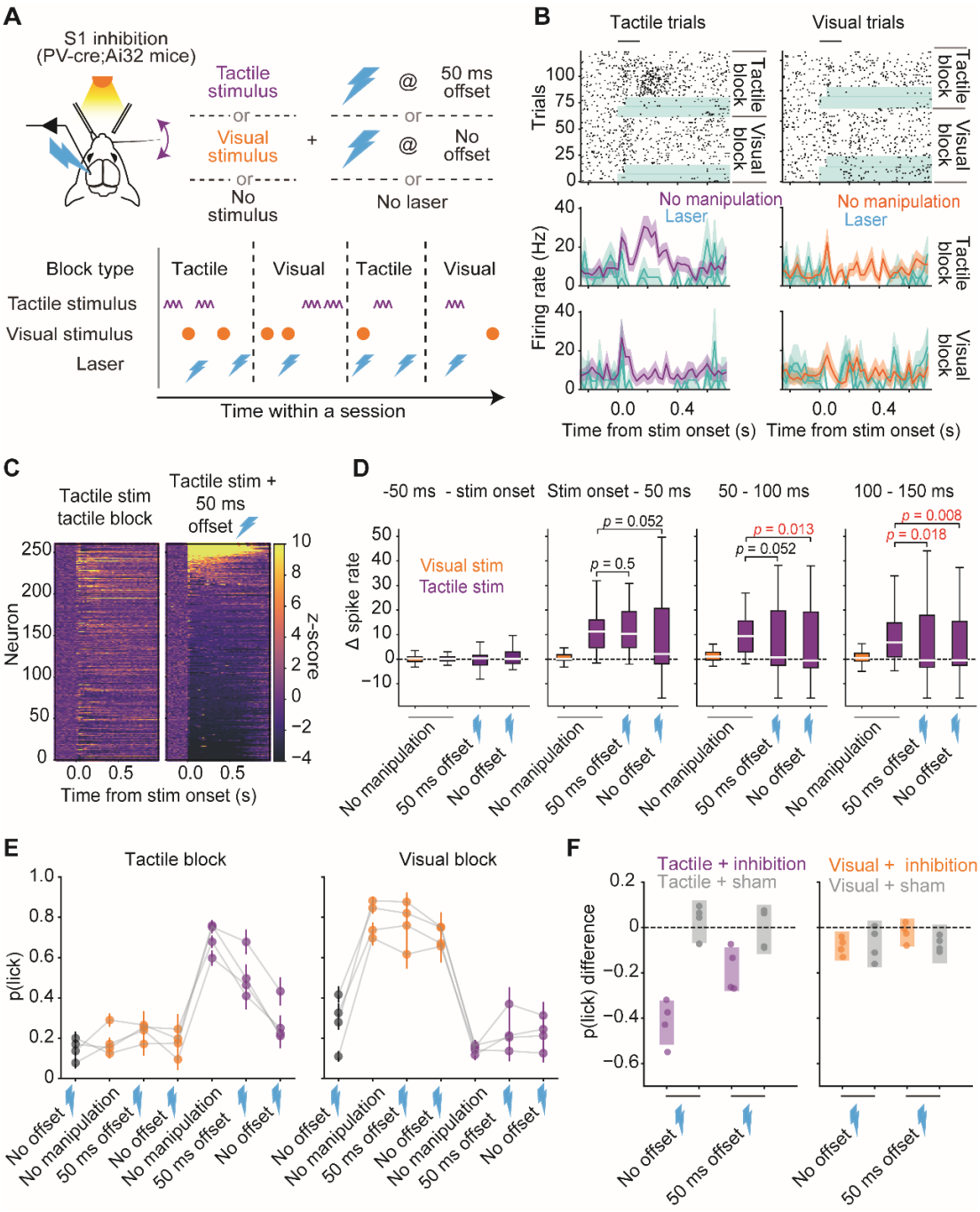

Figure 15. Inhibiting sensory-motor activity in S1 selectively impairs tactile detection.

(**A**) Schematic of experiment. In 30% of test-session trials the tactile or visual stimuli coincided with optogenetic inhibition of S1 activity that began simultaneously or with a 50 ms offset relative to the onset of the sensory stimulus. (**B**) Raster plots and PSTHs (mean ± sem) for an example neuron during inhibition trials or normal tactile and visual trials (blue highlights indicate period of optogenetic inhibition). (**C**) Heatmap of z-scored activity across all neurons recorded (n = 261 from

4 mice). (**D**) Change in spike rate relative to baseline for neurons with a significant positive-going SP (> 0.5) in tactile blocks. The effect of the optogenetic inhibition was delayed in the "50 ms laser offset" condition relative to the "No offset" condition, as expected, thereby preserving the initial touch-evoked spike rate change (black vertical lines: medians; boxes: IQR; whiskers: 1.5 x IQR; outliers are excluded for clarity). (**E**) Behavioral effects of optogenetic inhibition of S1 for different trial types within tactile (left) or visual (right) blocks. Inhibition of S1 during tactile stimuli in tactile blocks led to a decrease in the probability of licking. Inhibition of S1 during a visual stimulus in visual blocks did not significantly affect the probability of licking. Error bars: ± sem. (**F**) Left, quantification of the difference in p(lick) after tactile + inhibition trials vs tactile (no manipulation) trials (data indicated by brackets from left panel in (E)). Sham trials are taken from days in which mice underwent the same experiment as in (A) but with laser illumination of S1 obstructed. Right, similar to left panel but comparing p(lick) after visual + inhibition trials vs visual (no manipulation) trials (data indicated by brackets from right panel in (E)). Shaded regions indicate 95% CIs on Δ p(lick)

During tactile blocks, detection of tactile stimuli was reduced following both simultaneous and, to a lesser extent, delayed inhibition of S1 (Figure 14E,F). In contrast, S1 inhibition had a negligible impact on detection performance during visual blocks (Figure 14E,F). Task performance was therefore severely impaired by S1 inhibition during tactile but not visual blocks.

Together with our results from S1 excitation experiments (Figure 13), these inhibition data indicate that task performance depends on sensory-motor activity in S1 in a context-specific manner.

Discussion

We developed a cross-modal attention task for head-fixed mice, in which mice flexibly switched between responding to tactile stimuli while ignoring visual distractors, or responding to visual stimuli while ignoring tactile distractors. Identical tactile and visual stimuli served as targets and distractors; the only distinction between a target and distractor was the action required in response to its presentation. Our task was inspired by a cross-modal attention task used with monkeys, and by the finding that when monkeys attend to touch rather than vision, the responses to tactile stimuli in S1 cortex were enhanced (Hsiao et al., 1993).

Our task was designed to study the neural basis of flexible sensory-motor transformations from touch to different actions, depending on context. We found a prominent role for motor signals in shaping S1 activity (Figures 4-12). Our study used passive whisker stimulation in part to avoid the complexity of active touch tasks, in which rodents move their whiskers to generate tactile input (e.g. Isett, Feasel, Lane, & Feldman, 2018; Knutsen, Pietr, & Ahissar, 2006; Mehta, Whitmer, Figueroa, Williams, & Kleinfeld, 2007; O'Connor et al., 2010; von Heimendahl, Itskov, Arabzadeh, & Diamond, 2007). Indeed, mouse whisker S1 cortex controls active whisker retractions via projections to brainstem premotor nuclei (Auffret et al., 2018; Matyas et al., 2010). Our results highlight the sensory-motor nature of touch, and reinforce earlier findings on motor→sensory influences in rodent S1 (Petreanu et al., 2012; Ranganathan et al., 2018; Xu et al., 2012).

Optogenetic stimulation of the tongue premotor region ALM enhanced activity in S1 but did not depend on overt licking or movement. This supports the idea that motor signals we observed in S1 during our task could arise in part from frontal motor regions (Figure 13). However, the decision to emit a lick in response to our tactile or visual stimuli must be informed by information originating in sensory areas. For tactile stimuli, information likely flows from somatosensory cortex forward to frontal regions (de Lafuente & Romo, 2006; Guo et al., 2014) , but especially for weak stimuli such as ours, may be amplified by propagation in loops between different somatosensory (Kwon et al., 2016; Yang et al., 2016) and motor (Manita et al., 2015) areas.

Optogenetically adding S1 activity promoted licking during tactile but not visual blocks in our task, indicating not only that S1 activity is read out to support task performance (Sachidhanandam et al., 2013), but that this occurs in a context-specific manner. Prior work used optogenetic excitation of layer 4 neurons in particular whisker barrels that either corresponded to (the C2 barrel), or did not correspond to (the E3 barrel), the whisker mice used to solve an active tactile localization/detection task (O'Connor et al., 2013). Stimulation of the C2 but not E3 barrel "fooled" the mice into responding as though the whisker had actively touched an object, but only during epochs of active whisking. A context-specific readout of S1 activity may therefore be a common feature of different whisker-based tasks.

We optogenetically inhibited S1 and found that performance was degraded in tactile blocks but impacted at most negligibly during visual blocks. Moreover, by silencing throughout the full period of stimulus delivery, or only beginning 50 ms after stimulus

onset (see also: (Sachidhanandam et al., 2013)), we found that even late sensory-motor activity impacted task performance in a context-specific manner. These results support earlier work demonstrating an impact of late activity on tactile detection (Sachidhanandam et al., 2013). They also add to a growing body of work showing that transient optogenetic silencing of rodent somatosensory cortex impairs performance on whisker-based detection and similar tasks (Guo et al., 2014; Hong et al., 2018; Kwon et al., 2016; O'Connor et al., 2013; Sachidhanandam et al., 2013; Yang et al., 2016). However, rodents can learn to perform detection tasks in the absence of barrel cortex (Hong et al., 2018; Hutson and Masterton, 1986), suggesting that while mice readout activity from S1 cortex during our task, circuits for such sensory-motor transformations are redundant and/or capable of flexible remapping.

Enhanced S1 activity reflects motor actions and promotes stimulus processing and detection.

Here we found enhanced evoked firing in S1 when mice responded to, rather than ignored, tactile stimuli. These larger responses were associated with the licking action (behavioral choice) required of the mouse to report the tactile stimuli, similar to prior work using simple whisker-based tactile detection tasks (Kwon et al., 2016; Le Merre et al., 2018; Sachidhanandam et al., 2013; Takahashi et al., 2016; Yamashita & Petersen, 2016; Yang et al., 2016). These findings resemble the effects of attention and choice on the firing rates of neurons in the visual and somatosensory cortices of monkeys, perhaps suggesting a similar mechanism (Britten et al., 1996; Hsiao et al., 1993; Nienborg & Cumming, 2006, 2009; Steinmetz & Moore, 2014).

Recent work has emphasized the role of movements in shaping brain activity, and highlighted that movements uncontrolled by the experimenter can correlate with neuronal activity (Musall, Kaufman, Gluf, & Churchland, 2018; Steinmetz, Zatka-Haas, Carandini, & Harris, 2018; Stringer et al., 2019). We made no effort to dissociate attention from movement. We find that sensory and motor activity combine synergistically to enhance activity and thus may in fact be one mechanism that underlies a form of attention. Indeed, attention and movements normally co-vary (Moore & Zirnsak, 2017); pure dissociations between attention and movements, which occur during "covert" attention, are likely the exception rather than the rule. Indeed even when monkeys are trained to fixate and covertly attend to a stimulus, firing rate modulations in visual cortex occur only in conjunction with microssacades made in the direction of the attended stimulus (Lowet et al., 2018).

Optogenetic microstimulation of tongue premotor cortex (ALM) in naïve (untrained and not water restricted) mice drove activity in S1 that mimicked the motor-related activity we observed in our task. This result is consistent with the view that tongue premotor cortex can orchestrate widespread motor-related signals across cortex in mice (Allen et al., 2017; Chen et al., 2017; Makino et al., 2017). However, we found this to be true even at stimulation intensities subthreshold for evoking overt (out of the mouth) tongue movements, and prior to movements that could be recorded using our stress sensor (Figure 13 and Experimental Procedures). This experiment was inspired by work in primate (Armstrong & Moore, 2007; Moore & Armstrong, 2003; Moore et al., 2003; Moore & Fallah, 2001) and avian gaze control systems (Mysore et al., 2010; Mysore, Winkowski, & Knudsen, 2008; Mysore & Knudsen, 2014; Winkowski & Knudsen, 2007). Our results extend this line of work and suggest that engagement of orofacial premotor circuits enhance

S1 activity and thus could be facilitating stimulus processing in somatosensory cortex when mice ultimately detect a tactile stimulus. This interpretation would be consistent with a premotor theory of attention.

Optogenetic excitation of ALM (or M2) at levels sufficient to evoke tongue movements has been shown using widefield calcium imaging to evoke widespread patterns of activity across the dorsal surface of cortex during tasks that require go/no-go execution of a specific movement (Allen et al., 2017; Chen et al., 2017; Makino et al., 2017). The widespread nature of the licking-evoked response in these studies raise the question of whether this activity has any specificity in contributing to top-down effects on stimulus processing. Our electrophysiological experiments during a task that required distinct movements (i.e. directional licking), together with our ALM optogenetic stimulation results, support this prior work. However, we also reveal a layer of specificity that suggests that interactions between sensory and motor activity in S1 could have a disproportionate role in promoting stimulus detection. In particular, we find that motor-related activity occurs in a subset of neurons that partially overlaps with a subset of neurons encoding the tactile stimulus. Notably, the motor-related activity occurs earlier and stronger in neurons that also code for the tactile stimulus. Since we also show that optogenetically adding S1 activity causes trained mice to report the detection of a tactile stimulus, the exceptionally strong activity that occurs when neurons encode sensory and motor activity simultaneously likely has a stronger influence on the successful detection of the tactile stimulus than neurons that encode the motor-related activity alone.

As outlined earlier, the designs of some of the experiments and many of our main findings are similar to those of studies in the monkey and owl premotor attention literature,

however notable differences do exist. For example, while S1 activity is enhanced whenever a mouse licks, V4 neuron activity is only enhanced if monkeys pay attention to a stimulus that is located in or near the neurons receptive field and the stimulus must be of a type (ie orientation) that is able to cause the neuron to fire in the first place (Moore et al., 2003). Another important difference surrounds the anatomical and functional properties of FEF and how they differ from those of ALM. FEF projects to and receives projections from V4 (Ninomiya, Sawamura, Inoue, & Takada, 2012; Ungerleider, Galkin, Desimone, & Gattass, 2008), a region often recorded from in attention studies. FEF controls eye movements, the part of the body that is directly involved in sampling stimuli that were relevant in those experiments. Furthermore, microstimulation of FEF (or AGF in owls) was done in areas controlling saccades to stimuli within the RFs of recorded V4 neurons (Armstrong, Fitzgerald, & Moore, 2006; Armstrong & Moore, 2007; Moore et al., 2003). ALM on the other hand does not project strongly to and does not receive strong projections from barrel cortex (Oh et al., 2014). ALM has also primarily been shown to control tongue and jaw movements, parts of the body that are not directly involved in sampling the relevant stimuli. Finally, suprathreshold stimulation of ALM does not lead to movements that are spatially aligned to the location of the sensory stimulus in our task. As a result of these differences it is less clear how ALM might be exerting top-down influence on sensory processing in S1. It would be important to explore further whether the evoked activity in S1 by ALM stimulation serves a similar pre-motor attention role as FEF. This would significantly expand the premotor theory of attention to include arbitrary stimulus-response associations and not just those where stimulus sampling and response movements are carried out by the same body part.

One recent study gives some evidence that eye movements and movements not involving the oculomotor system could be exerting similar top-down effects on early sensory cortex. Abdolrahmani and colleagues trained mice to perform a visual orientation discrimination task that required them to spin a wheel in one direction or another (Abdolrahmani, Lyamzin, Aoki, & Benucci, 2019). Widefield calcium imaging as well as wheel and eye movement recordings showed that stimulus evoked activity was dramatically increased whenever the mice made movements of either kind. Furthermore, when eye and wheel movements occurred at approximately the same time, the resulting activity was a sublinear sum of that seen when either of the two movements were made alone. Importantly, this addition of motor related activity was correlated with task performance such that high performance was associated with almost linear summation of motor related activity. These results suggest that stimulus evoked activity in sensory cortex is similarly enhanced by top-down inputs from motor regions that control distinct body movements and that these inputs can have a compounding effect on behavioral performance when they occur simultaneously.

Alternative sources for enhanced S1 activity during stimulus detection

While the above discussion suggests an intercortical mechanism of attention involving frontal premotor regions acting on sensory cortices, other recent work provides an alternative less direct mechanism that emphasizes the role of thalamus. In a similar cross-modal attention task in mice, neurons in the lateral geniculate nucleus (LGN) were shown to have modulated firing rates both during anticipation and presentation of attended visual stimuli (Wimmer et al., 2015). As in our task, mice attended to stimuli in one

modality while ignoring distractors in another modality (in this case auditory and visual). However, unlike our task, the behaviorally relevant modality could switch on a trial by trial basis rather than in blocks. This was accomplished by presenting a cue followed by a delay (anticipation period) prior to stimulus onset. Optogenetic inhibition of LGN and prefrontal cortex (PFC) or activation of visual thalamic reticular nucleus (visTRN) during the anticipation and stimulus presentation period significantly degraded task performance. While neurons in sensory cortex were not recorded during the task, inhibition of visual cortex only impaired task performance during the presentation of visual stimuli. This was presumed to be due to blocking any and all cortical processing of the visual stimulus. The authors concluded that PFC-mediated attention effects primarily act on thalamic rather than cortical processing of sensory stimuli in their task.

The results from the above study support a well-known (Halassa & Kastner, 2017; Saalmann & Kastner, 2011) role of thalamus as a critical brain structure involved with attentional selection of sensory stimuli however they do not preclude the necessity of attention effects in cortex for enhanced sensory processing. The finding that inhibition of sensory cortex is ineffective at disrupting task performance during anticipation periods may indicate a more circumscribed period for attentional effects in cortex. Alternatively, this may be due to the structure of the task whereby the specific motor response (ie movement direction) that is required is unknown to the mouse until stimulus presentation. This would make it less likely that pre-motor sources of attention would be beneficial for sensory processing during these periods. In our task, the behavioral relevance of a stimulus is also tied to a specific motor action (ie tactile blocks → lick to the right). Therefore, the required action is known to the mouse before the stimulus is presented. It would be interesting to

see if inhibition of S1 prior to stimulus presentation in our task disrupts task performance. Furthermore, attentional modulation of sensory cortical firing is often observed >50 ms after stimulus onset (Buffalo et al., 2010). Thus, because visual cortex was inhibited for the duration of the visual stimulus presentation it likely did not selectively target top-down attentional effects. Inhibition of visual cortex after a short delay would allow for early sensory processing to occur while disrupting much of the attentional modulation that would normally follow. In our task, mice are able to detect brief (50 ms) stimuli. Disrupting activity during motor related modulation but after the earliest sensory evoked activity is allowed to occur still disrupts performance in our task. From these results, I speculate that attending to a stimulus likely consists of multiple subprocesses that target different critical sensory regions and at different periods surrounding the onset of stimuli. Furthermore, different tasks may emphasize different attentional subprocesses.

We report that enhanced neural responses correlate with mice licking a reward port, as described earlier. This correlation suggests that this enhanced activity is likely a motor-related signal. However, one alternative interpretation is that they could be reflecting the receipt or expectation of reward since these are normally also associated with the licking response. Furthermore, signals related to reward and its expectation have been observed in rodent primary sensory cortex (Chubykin, et al., 2013; Lacefield et al., , 2019; Shuler & Bear, 2006). However, our data argue against this possibility. The choice-related activity in our task cannot be explained by the receipt of reward since it was also observed in trials where the mouse erroneously licked for a tactile or visual stimulus but in the wrong block of trials (Figure 4; False alarm trials). Furthermore, it is unlikely that it can be explained

by the expectation of reward since the activity differed based on which spout the mouse licked even though both gave equal rewards.

Stimulus and motor activity interact synergistically in S1

Our results demonstrate that S1 is a cortical locus where sensory and motor related activities overlap. Importantly, several key results from our experiments suggest that these signals interact and are not represented orthogonally. These observations add to prior work investigating the importance of sensorimotor interactions for sensory processing in mouse somatosensory cortex (Petreanu et al., 2012; Ranganathan et al., 2018; Xu et al., 2012; Manita et al., 2015).

We found that S1 neurons on average predicted contraversive better than ipsiversive licking (Figure 5). Remarkably, individual S1 neurons discriminated the direction of licking, with a preference for contraversive licking, in response to tactile but not visual stimuli (Figure 9C,D and Figure 12) . Sensory activity therefore interacts differently with motor signals relating to distinct movements.

Both somatosensory and motor processing are hemispherically lateralized, with extensive bidirectional connections between whisker S1 and whisker motor cortex (Aronoff et al., 2010; Mao et al., 2011) . The contraversive bias we observed may therefore be due to synergistic interactions among sensory and motor circuits localized to the same hemisphere. I speculate that this synergy arises because innocuous touch-driven movements typically facilitate further interactions with touched objects (as opposed to driving avoidance). Moreover, psychophysical work has shown faster reaction times for

movements made on the same side of the body as the sensory stimuli that provoke them (Clarke & Zaidel, 1989; Marzi, Bisiacchi, & Nicoletti, 1991; Muram & Carmon, 1972; Tamè & Longo, 2015).

One explanation for why licking-related activity did not differ for visual stimuli is due to the lack of visual stimulus responses in S1 We used ideal-observer analysis to quantify how well single S1 neurons discriminated the presence vs absence of stimuli and the licking responses of the mouse. Individual S1 neurons signaled the presence of the tactile stimuli, as expected, but not visual stimuli (Figure 7A). While visual responses have been observed in mouse whisker S1 (Zhuang et al., 2017), a feature of our task is that mice had to ignore visual stimuli when responding to tactile stimuli. The need to keep tactile and visual behavioral responses separated may promote their segregation at the neural level. If sensory and motor responses are synergistically interacting in S1 to produce higher firing rates when mice lick contraversively to tactile stimuli, a lack of visual responses in S1 neurons would preclude such synergy during visual contraversive licking.

Further evidence for sensory and motor activity acting synergistically in our data is reflected in the subset of stimulus coding neurons that also predicted the lick response of the mouse. As previously discussed, this subset showed earlier and stronger discrimination of choice compared with neurons that predicted the lick response but did not encode the whisker stimulus (Figure 8A-B). These results suggest, that sensory and motor signals interact to boost activity at the single neuron level. In principle this enhanced activity could then lead to a higher probability of the mouse detecting the stimulus. However, it is not known whether earlier and stronger choice-related activity is specific to neurons that encode behaviorally relevant stimuli. For example, it may be the case that

stimulus responsive neurons receive stronger inputs from motor regions regardless of whether the stimulus they are responsive to is a rewarded stimulus. If so then it seems unlikely that this sensorimotor interaction is what underlies a mouse's ability to detect behaviorally relevant stimuli since motor and sensory activity would combine synergistically even for unimportant stimuli. One experiment that could clarify this point would be to record simultaneously from more than one barrel column. Mice could be trained to detect the deflection of one whisker during training but then receive deflections of either whisker during testing. If neurons encoding the rewarded stimulus show earlier and stronger DP than those that encode the non-rewarded stimulus, this would suggest that plasticity of motor inputs is enhanced for behaviorally relevant stimuli. Additionally, another cohort of mice could be trained to detect deflections of one whisker but ignore deflections of the other. If the probability of licking for a stimulus depends on DP occurring early and robustly in neurons encoding a whisker stimulus, then it would be adaptive to reduce choice-related activity in neurons that encode irrelevant stimuli while enhancing choice-related activity in neurons that encode relevant stimuli. One study showed results that approach this but in corticostriatal projections from auditory cortex (Xiong, Znamenskiy, & Zador, 2015). After training, corticostriatal projections from neurons encoding behaviorally relevant frequencies were stronger than those encoding non-behaviorally relevant frequencies. This difference presumably underlies increased task performance as training progresses.

Sensory and motor encoding in S1 could engage striatal circuits that mediate Go/No-Go responses

The sensorimotor activity in S1 when mice correctly detect tactile stimuli in our task is remarkably similar to that shown by direct-pathway medium spiny neurons in the dorsolateral striatum. The direct pathway is known to facilitate movement or "Go" responses. Conversely, the indirect pathway is known to inhibit movement resulting in "No-Go" responses. In a study by Sippy and colleagues (Sippy, Lapray, Crochet, & Petersen, 2015), optogenetically activating direct pathway but not indirect pathway medium spiny neurons in a part of the dorsolateral striatum that receives projections from barrel cortex caused robust licking in mice trained to detect a whisker stimulus. During correct detection of the whisker stimulus, direct pathway medium spiny neurons showed an early sensory evoked phase of activity (0-50 ms after stimulus onset) followed by a phase of prolonged motor-related activity (>50 ms after stim onset), a pattern that was similar to a subset of S1 neurons in our data. Interestingly, indirect pathway medium spiny neurons did not show early sensory evoked activity but did show motor-related activity, a pattern that was similar to a different subset of neurons in our data. These results suggest that combined sensory and motor activity originating from barrel cortex, at least in part, drives licking responses for detection of a whisker deflection. If direct and indirect pathways are in opposition, the faster, robust sensorimotor activity occurring in direct pathway medium spiny neurons may tip the balance in favor of "go" responses that ultimately lead the mouse to correctly detecting the stimulus. This aligns well with our finding that neurons showing the fastest DP onset were those that also showed strong sensory evoked activity or SP. It would be interesting to confirm if corticostriatal neurons that combine sensory and motor related activity preferentially project to direct pathway

medium spiny neurons while those that only show motor related activity project to indirect pathway medium spiny neurons. If this were true, I speculate that the synergistic effect of combining tactile and motor related responses in the subset of corticostriatal neurons that project to direct pathway medium spiny neurons are contributing to overcoming the opposing effect of the slower indirect pathway activation when mice correctly detect tactile stimuli in our task. Importantly, we also observed that motor-related activity was prominent in barrel cortex when mice detected a visual stimulus. However, I speculate that since no tactile stimulus activity was present in these trials, the same direct pathway neurons that mediate tactile-lick responses were not activated early and strongly enough to overcome indirect pathway neurons. Thus, the mice did not lick the reward port associated with the tactile stimulus. Instead, I presume that in these trials corticostriatal neurons in visual cortex synergistically combined visual stimulus and motor related activity to drive relevant direct pathway medium spiny neurons that correspond to 'go' responses for licking the reward port associated with the visual stimulus. This would lead to correct visual stimulus detection in visual stimulus hit trials in our task.

Conclusion

Together, our results show that sensory and motor activity interact in mouse S1 during a cross-modal attention task to promote tactile detection, and that the consequences of sensory-motor activity in S1 depend on action context. These findings support a pre-motor theory of attention and highlight the essential role of motor intentions on tactile processing.

Table 1

Mouse ID	Sex	Mouse Line	Date of birth	Test Session Dates	Figure appearances
EF0074	M	Som-Cre; Ai32	06/30/15	12/27/15 - 01/27/16	Figs 2B(top); 3A-C; 4C; 5A-H; 6A-D, 7A,B; 8 A,B
EF0076	M	PV-Cre	09/20/15	02/11/16 - 03/07/16	Figs 2A, B(middle); 3A-C; 4C; 5A-H; 6A-D, 7A,B; 8 A,B
EF0077	M	PV-Cre; Ai32	09/20/15	04/20/16 - 05/12/16	Figs 3A-C; 4C; 5A- H; 6A-D, 7A,B; 8 A,B
EF0079	M	Som-Cre; Ai32	11/28/15	02/24/16 – 03/24/16	Figs 3A-C; 4B,C; 5A-H; 6A-D, 7A,B; 8 A,B
EF0081	M	PV-Cre; Ai32	02/01/16	04/23/16 - 05/26/26	Figs 3A-C; 4C; 5A-H; 6A-D, 7A,B; 8 A,B
EF0083	M	Som-Cre; Ai32	01/10/16	05/25/16 – 06/16/16	Fig 3A-C
EF0084	M	PV-Cre; Ai32	02/21/16	06/24/16 - 07/26/16	Figs 3A-C; 4C;5A-H;6A-D, 7A,B; 8 A,B
EF0085	M	Som-Cre; Ai32	02/21/16	08/02/16 - 08-24-16	Fig 3A-C
EF0088	M	PV-Cre; Ai32	03/10/16	07/16/18 - 01/13/16	Figs 3A-C; 4C;5A-H;6A-D, 7A,B; 8 A,B; 9B-D; 10A-D; 11A-B
EF0089	M	Som-Cre; Ai32	02/14/16	08/19/16 - 09/14/16	Figs 2B(bottom); 3A-C; 4C;5A-H; 6A-D, 7A,B; 8 A,B
EF0091	M	Som-Cre; Ai32	08/05/16	03/21/17 - 04/13/17	Figs 12A-C
EF0094	M	Som-Cre; Ai32	09/01/16	03/27/17 - 04/27/17	Figs 9B-D; 10A-D; 11A-B
EF0098	M	Som-Cre; Ai32	11/15/16	04/06/17- 04/28/17	Figs 9B-D; 10A-D; 11A-B
EF0099	M	Som-Cre; Ai32	11/15/16	03/01/17 - 03/23/17	Figs 12A-C
EF0101	M	Som-Cre; Ai32	4/3/17	08/31/17 – 09/21/17	Figs 12A-C
EF0102	M	Som-Cre; Ai32	4/3/17	08/15/17 - 09/05/17	Figs 12A-C
EF0114	M	PV-Cre; Ai32	12/25/17	05/2/18 - 06/1/18	Figs3A-C; 4C;5A-H; ; 6A-D;, 7A,B; 8 A,B; 15B-F
EF0131	M	PV-Cre; Ai32	03/10/18	07/01/18 - 08/08/18	Figs 15C-F
EF0132	M	PV-Cre; Ai32	03/10/18	07/08/18 - 08/14/18	Figs 15C-F
EF0139	M	Emx1-Cre; Ai32	5/20/18	07/13/18	Figs 13B,C
EF0143	M	Emx1-Cre; Ai32	5/01/18	08/30/18	Figs 13C
EF0144	M	PV-Cre; Ai32	05/07/18	08/13/18- 08/30/18	Figs 15C-F
EF0146	M	Emx1-Cre; Ai32	05/01/18	09/01/18	Figs 13C

EF0147	**M**	**Emx1-Cre; Ai32**	**06/27/18**	**11/27/18 – 12/17/18**	**Figs 14B**
EF0148	**M**	**Emx1-Cre; Ai32**	**06/27/18**	**12/10/18 - 12/17/18**	**Figs 14B**
EF0149	**M**	**Emx1-Cre; Ai32**	**06/27/18**	**12/08/18 - 12/17/18**	**Figs 14B**
EF0150	**M**	**Emx1-Cre; Ai32**	**06/27/18**	**12/13/18 12/28/18**	**Figs 14B**

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Nine years of experience in neuroscience and behavioral psychology research with expertise in data analysis, statistics, and scientific communication.

- Proficient in extracting meaningful insights from large datasets using modern programming languages.
- Experienced in designing and implementing neuroscience experiments involving mouse behavior and elecrophysiological recordings.
- Strong leadership and teamwork experience: mentored junior scientists and collaborated with teams in both scientific and business-related settings.
- Exceptional written and oral communicator: presented complex scientific concepts to a wide range of audiences.

SKILLS

Programming Languages and Software:

- *Proficient*: Python (numpy, pandas, matplotlib, scikit-learn, Jupyter), MATLAB, Adobe Illustrator, Microsoft Office.
- *Familiar*: Pytorch, Keras, SQL.

Machine Learning:

- *Proficient*: random forest, t-SNE, multivariate linear regression, logistic regression.
- *Familiar*: feed forward neural networks, convolutional neural networks, recurrent neural networks, support vector machines.

Laboratory skills:

- *Proficient*: behavioral task design, electrophysiology, tetrode microdrive implantation surgery, histology, animal husbandry, PCR, qPCR, western blotting, confocal microscopy

WORK AND RESEARCH EXPERIENCE

Graduate student researcher **08/2013 –Present**

The Solomon H. Snyder Department of Neuroscience
Johns Hopkins School of Medicine
Baltimore, MD

- Effectively used behavioral neuroscience and reinforcement learning theory to design and implement experiments that investigated the mechanisms of touch perception, sensorimotor integration, and attention.
- Implemented random forest and multivariate linear regression analyses using scikit-learn on time-series data.
- Collected, combined, and processed >10TB of data from multiple sources.
- Wrote custom data analysis libraries in Python and MATLAB that are used by multiple members of the laboratory.
- Used amazon AWS EC2 instance to cut down the compute time of key analyses by a factor of 10.

- Created data visualizations using t-SNE and matplotlib that resulted in the characterization of neural responses in behaving subjects.
- Presented experimental results to senior scientists from inside and outside my field at a major scientific conference.
- Recruited, mentored, and trained junior scientists that have gone on to pursue post-graduate degrees at prestigious institutions.

Pro-bono graduate student consultant **08/2018 – Present**
Johns Hopkins Graduate Consulting Club
Johns Hopkins School of Medicine
Baltimore, MD

- Worked with a team of graduate students to develop a strategy for increasing revenue for a local non-profit.
- Used Python to analyze relevant publicly available datasets in order to effectively extract insights that were crucial for informing strategy recommendations for the client.
- Designed a plan to take advantage of crowdsourcing as a novel stream of charitable funding that is expected to increase the client's yearly donations by 10-30%.

Research technician **09/2011 – 05/2013**
Department of Anatomy and Neurobiology
University of Maryland Baltimore
Baltimore, MD

- Designed and conducted behavioral and molecular biology experiments to investigate the neural causes of depression.
- Analyzed behavioral and molecular biology data using Excel.

Undergraduate research assistant **09/2009 – 05/2011**
Psychology Department
McGill University
Montreal, QC

- Designed and implemented behavioral neuroscience experiments to investigate the neural mechanisms of forming habit-based memories.

EDUCATION

PhD in Neuroscience
expected 2019
The Solomon Snyder Department of Neuroscience, Johns Hopkins School of Medicine
Advisor: Daniel H. O'Connor
GPA 3.77

BSc Honors Psychology, Minor Biology,
May 2011
Faculty of Science,
McGill University
GPA 3.75

PUBLICATIONS AND POSTER PRESENTATIONS

- **Finkel EA**, Chang YT, Lubin EE, Chang AJ, Cohen JY, O'Connor DH and O'Connor DH. Touch processing depends on action context. (In preparation)
- **Finkel EA** and O'Connor DH. Learning recruits higher cortical areas into rapid sensorimotor streams. Neuron. 2018 Jan 3;97(1):1-2.
- Francis TC, Chandra R, Friend DM, **Finkel EA**, Dayrit G, Miranda J, Brooks JM, Iñiguez S, O'Donnell P, Kravitz A, Lobo MK. (2015) Nucleus accumbens medium spiny neuron subtypes mediate depression-related outcomes to social defeat stress. Biological Psychiatry. 77:212-222
- **Finkel EA**, Lubin EE, Chang AJ, Cohen JY, O'Connor DH; Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD. Sensorimotor specificity of decision-related activity in somatosensory cortex. Program No. 667.19. 2018 Neuroscience Meeting Planner. San Diego, California: Society for Neuroscience, 2018. Online.

RELEVANT COURSEWORK

Graduate and undergraduate courses:

- Statistics, Experimental Design, Systems Neuroscience, Behavioral Neuroscience, Social Psychology, Cognitive Psychology, Programming for Scientists and Engineers, Calculus.

Coursera and other online courses:

- Deep Learning Specialization, Machine Learning, Fast.ai, Linear Algebra.

LANGUAGES

English (native), Spanish (proficient)